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'*meso*-Selective' functionalisation of *N*-benzyl-α-methylbenzylamine derivatives by α-lithiation and alkylation

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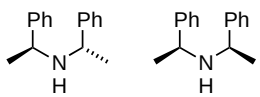
Abstract—Lithiation and methylation of amide and carbamate derivatives of α-methylbenzylamine proceeds with high diastereoselectivity in favour of *meso* bis-α-methylbenzylamine derivatives. Carboxylation of the intermediate organolithium is also diastereoselective, and with *N*-Boc *p*-methoxy-α-methylbenzylamine as starting material, oxidative cleavage provides a new asymmetric route to phenylglycine. Other electrophiles give a range of stereochemical outcomes, apparently depending on the stereospecificity of their reactions with a pair of diastereoisomeric organolithiums of low to moderate configurational stability.

(*R*,*R*)- and (*S*,*S*)-*N*,*N*-Bis(α-methylbenzyl)amine **1** and its derivatives are important reagents for asymmetric synthesis. Their lithium derivatives, for example, are among the most widely used and generally successful of the chiral lithium amide bases.[1] Amine **1** is made stereoselectively by reductive amination of the appropriate α-methylbenzylamine with acetophenone, a reaction which proceeds with 8:1 selectivity in favour of chiral stereoisomer **1** over the *meso* stereoisomer **2**.[2] Achiral **2** is by contrast much less useful, and rarely required,[3] and as a result there is no stereoselective route to **2** and its derivatives.

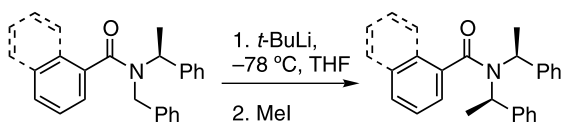


1 **2**

As part of a study[4] of stereospecificity in some cyclisation reactions,[5] we required both diastereoisomers of some amide derivatives of **1** and **2**. We therefore made amides **3** and **4** from α-methylbenzylamine and treated them with *t*-BuLi in THF at −78°C. Quenching the deep red organolithiums with methyl iodide after 2 h gave amides **5** and **6**.[6] We had expected to obtain both as a mixture of diastereoisomers, but surprisingly the *meso* diastereoisomer of both compounds was formed with high stereoselectivity (97:3 for **5** and 90:10 for **6**).[7] Good yields of both *meso* amides were isolated (Scheme 1). The stereochemistry of the products was indicated by their lack of optical rotation and by spectroscopic comparison with authentic samples of amides derived from **1**.

Though ideal for our purposes, using a chiral compound to make an achiral one, albeit stereoselectively, is of limited appeal. We therefore investigated the stereoselective synthesis of unsymmetrical benzylamine derivatives by the lithiation and alkylation of the amide **7** and the carbamate **8** with a range of electrophiles. Using a Carousel Reaction Station (Radleys Ltd.), samples of **7** and **8** were stirred with *t*-BuLi in THF at −78°C for 30–120 min and quenched in parallel with the electrophiles shown in Table 1 (Scheme 2). The product ratios (determined by NMR and HPLC) and the isolated yields are shown in Table 1.

Stereoselectivity varied according to the electrophile and was different for reactions of the amide **7** and the



benzamide **3**
1-naphthamide **4**

benzamide **5**, 77%
1-naphthamide **6**, 80%

Scheme 1. *meso*-Selective alkylation of amides.

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Table 1.

Entry	E^+	E	Yield **11** (%)	Ratio **11a**:**11b**	Yield **12** (%)	Ratio **12a**:**12b**
1	MeOD	D	88	97:3[a]	98	>98:2[a]
2	MeI	Me	80	97:3[b]	82[c]	96:4[b]
3	BnBr	Bn	84	>98:2[a]	68	50:50
4	AllylBr	Allyl	85	93:7[a]	70	50:50
5	CO_2	CO_2H	78	89:11[b]	–	–
6	$ClCO_2Me$	CO_2Me	90	98:2[b]	97[d]	>98:2[b]
7	Cyclobutanone		–	–	63	75:25[a]
8	Cyclohexanone		–	–	40	>98:2[a]
9	PhCH=NPh		–	–	87	[a,e]
10	Bu_3SnCl	$SnBu_3$	75	11:89[a]	67	36:64[b]

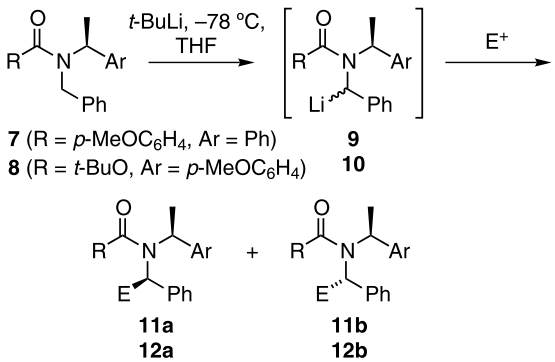
[a] Unconfirmed stereochemistry.

[b] Proven stereochemistry (see below).

[c] White solid, mp = 64–66°C, $[\alpha]_D^{25}$ −8 (c = 1.21); δ_H ($CDCl_3$, 300 MHz) 7.4–7.2 (7H, m, ArH), 6.91 (2H, d, J 8, ArH), 3.89 (3H, s, MeO), 1.2 (6H, b, CH_3), 1.12 (9H, s, Boc). δ_H (DMSO, 100°C, 300 MHz) 5.0 (1H, q, C*H*CH_3), 4.84 (1H, q, C*H*CH_3), 3.88 (3H, s, CH_3O), 1.35 (3H, d, CH_3), 1.33 (3H, d, CH_3), 1.25 (9H, s, Boc). m/z (CI) 356 (M+H$^+$, 15%), 300 (80%), 256 (20%), 125 (100%). Found M+H$^+$ 356.2227; $C_{22}H_{30}NO_3$ requires M, 356.2225. ν_{max}/cm^{-1} (film) 1686, 1512.

[d] Colorless oil. $[\alpha]_D^{23}$ +90.9 (c = 0.44); δ_H ($CDCl_3$, 300 MHz) 7.5–7.3 (7H, m, ArH), 6.9 (2H, d, J 9, ArH), 5.8 (1H, b, C*H*Me), 4.7 (1H, b, C*H*CO_2Me), 3.86 (3H, s, CH_3O), 3.62 (3H, b, CH_3OCO), 1.45 (9H, s, Boc), 1.3 (3H, d, J 7, C*H*$_3$CH). m/z (CI), 400 (M+H$^+$, 20%), 344 (55%), 300 (75%), 135 (100%). Found M$^+$ 399.2044; $C_{23}H_{29}NO_5$ requires M 399.20456. ν_{max}/cm^{-1} (film) 1748, 1691.

[e] 3:1 mixture of **13a**:**13b**.

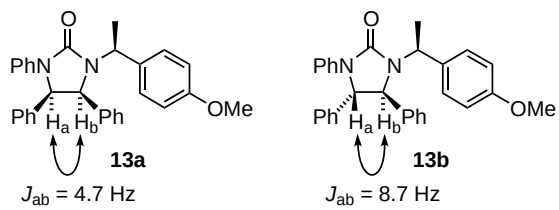


Scheme 2. Diastereoselective lithiation and electrophilic quench of *N*-benzyl-*N*-α-methylbenzyl derivatives.

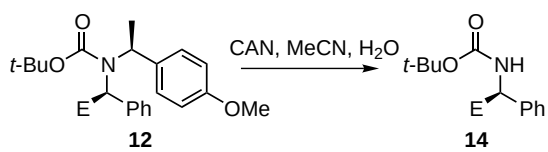
carbamate **8**. However, methylation and carboxylation were highly stereoselective with both starting materials, and treatment of **12a** (E = Me) with ceric ammonium nitrate in aqueous acetonitrile gave the *N*-Boc-α-methylbenzylamine **14** (E = Me), whose optical rotation[8] confirmed the overall sense of stereoselectivity in the alkylation (Scheme 3 and Table 2).

Deprotection of **12a** (E = CO_2Me) under the same conditions provided a new synthesis of the (*R*)-*N*-Boc-phenylglycine methyl ester **14** (E = CO_2Me)[9] and the optical rotation[10] confirmed the sense of stereoselectivity of the acylation with methyl chloroformate (Table 2). Mixtures of diastereoisomers of **12** (E = allyl) and **12** (E = benzyl) were deprotected in the same way to give racemic samples of **14** (E = allyl, E = benzyl).

Methylation of the product of carboxylation of **7** with CO_2 gave material identical with that produced by methoxycarbonylation of **7** with $ClCO_2Me$, proving



that the reactions in Table 1 (entries 5 and 6) proceed with the same stereochemical sense. We therefore assign stereochemistry to **11a** (E = CO_2H and E = CO_2Me) on the assumption that **7** follows **9** in its reaction with $ClCO_2Me$. However, the stereoselectivity of deuteration (entry 1), benzylation (entry 3), allylation (entry 4), and reactions with ketones and imines (entries 7–9) have not been confirmed and stereochemistry of the products is assigned arbitrarily. Two imidazolinones **13a** and **13b** were produced on reaction of **10** with *N*-phenylbenzaldimine by cyclisation of the newly-formed amide anion onto the Boc group. Stereochemistry is assigned on the basis of their J_{ab} coupling constants, the significant difference in the values of these coupling constants suggesting that the compounds differ in stereochemistry only at the C=N-derived stereogenic centre. The stereoselectivity of stannylation (entry 10) is opposite to that of deuteration, as explained below.



Scheme 3. Oxidative deprotection of *N*-α-methyl-*p*-methoxybenzyl derivatives.

Table 2.

Entry	E	Yield **11** (%)[a]	$[\alpha]_D$	$[\alpha]_D^{lit.}$
1	Me	80	−52[b]	−62[8]
2	Bn	79	0	–
3	Allyl	47	0	–
4	CO_2Me	41	−112	−132.3[10]

[a] From crude mixture of **12a**+**12b**.
[b] 92% ee by HPLC on chiral stationary phase.

The stereoselectivity of the lithiation–alkylation sequence, or lack of it, must originate from factors which may include the diastereoselectivity of the deprotonation of **7** and **8**, the rate at which the two diastereoisomers of the organolithiums **9** and **10** interconvert (their configurational stability), the relative stability of the two diastereoisomers of **9** and **10**, and the rate and stereospecificity with which each reacts with the electrophile. We carried out a series of experiments aimed at disentangling these various factors.[11]

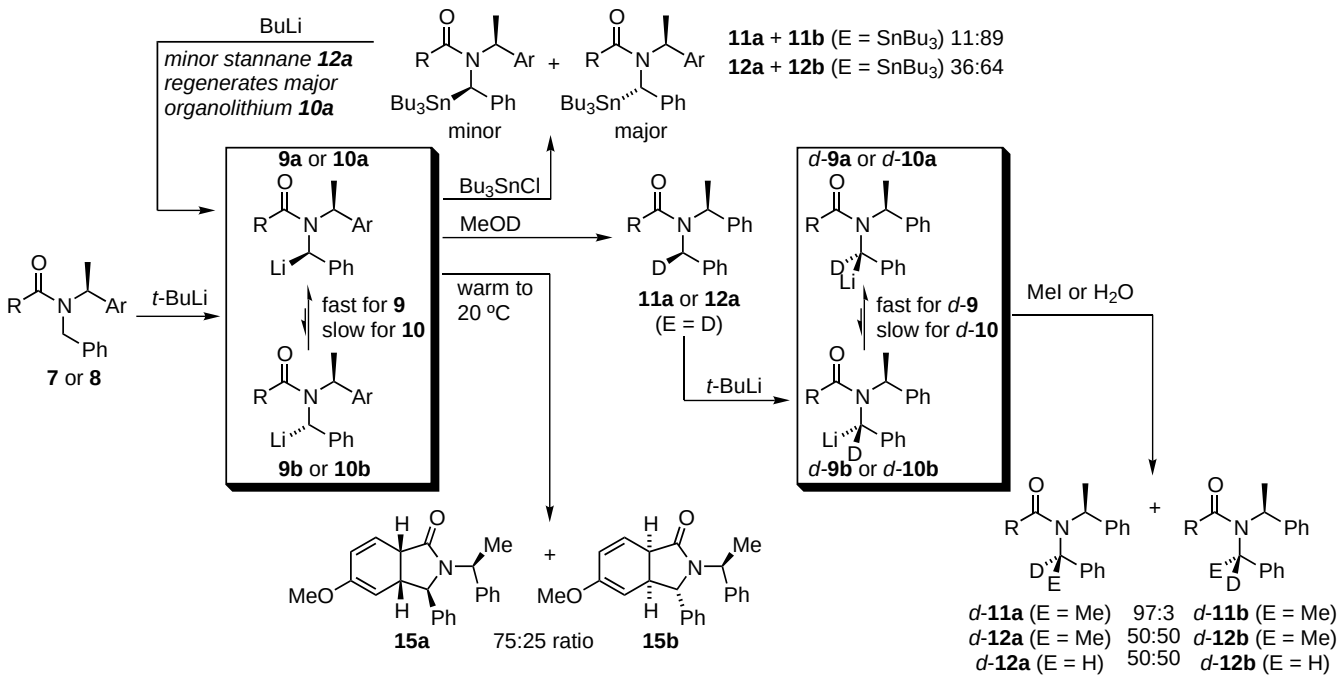
To establish whether the intermediate organolithiums are configurationally stable, the deuterated compounds **11a** and **12a** (E = D) were re-deprotonated with *t*-BuLi at −78°C and quenched with MeI and, for **12a** (E = D), with NH_4Cl. Mass spectrometry showed that >98% of the product in each case remained deuterated, showing that only the ^1H atom had been removed from **11a** and **12a** (E = D). This result is in accord with the high values typical of primary kinetic isotope effects in low temperature lithiations.[12] However, while methylation of lithiated **11a** (E = D) returned *d*-**11a** (E = Me) as a single diastereoisomer, methylation or protonation of lithiated **12a** (E = D) returned *d*-**12a** and *d*-**12b** (E = Me) or **12a** and **12b** (E = D) as a 50:50 mixture (Scheme 4).

As far as is known, deprotonation to form an organolithium and reprotonation of the organolithium occur with reliable retentive stereospecificity,[13] so the lack of stereospecificity in the deprotonation–reprotonation of **12a** must be due to a lack of configurational stability in **10**. Nonetheless, the lack of configurational stability in **10** cannot be complete, because methylation of **10** produced by lithiation of **8** gives a different stereochemical outcome from methylation of *d*-**10** produced by lithiation of **12a** (E = D). Organolithium **9**, by contrast, appears to have no configurational stability on the reaction timescale, since methylation or protonation (deuteration) of **9** formed by lithiation of either **7** or **11a** (E = D) gives the same outcome (Scheme 4).[14]

These results are consistent with a common mechanism in which the stereoselectivity of the lithiation-quench of **7** and **8** is determined by kinetic and thermodynamic factors combining to yield a single diastereoisomer of organolithiums **9** and **10**. For **9**, equilibration to a single diastereoisomer is fast, disguising the initial stereoselectivity of the lithiation, but slower equilibration of **10** suggests that the initial kinetic stereoselectivity of the deprotonation is high. The single diastereoisomer of **9** or **10** must then react with varying stereospecificity to yield the observed product ratios.

On warming, **9** undergoes a cyclisation to give **15** in a 3:1 ratio of diastereoisomers.[15] The cyclisation is effectively an internal electrophilic quench, but it takes place only at temperatures above −40°C, suggesting that at higher temperatures the thermodynamic selectivity in favour of **9a** is decreased.

We tried to observe the stereoselectivity of the deprotonation of **10** directly by ^1H NMR spectroscopy, carry-



Scheme 4. Investigating the origin of the stereoselectivity.

ing out the lithiation in d_8-THF in an NMR tube. At −78°C, the starting material **8** was clearly a mixture of N–CO rotamers, but lithiation gave a 85:15 mixture of two species, presumably the two diastereoisomers of **10** formed under kinetic control. Under the same conditions, *d*-**12a** gave the same two species, but with a considerably higher proportion (30–40%) of the minor diastereoisomer. The latter result, and therefore possibly also the former, must represent an already partly epimerised mixture of organolithiums **10**.

Similar conclusions about configurational stability can be drawn from reactions of the stannylated compounds **11** (E = $SnBu_3$) and **12** (E = $SnBu_3$). The 89:11 mixture of **11b** and **11a** (E = $SnBu_3$) was transmetallated with BuLi and the product organolithium was methylated. **11a** (E = Me) was obtained with 97:3 stereoselectivity: the stereochemistry of the starting stannanes has no bearing on the stereochemistry of the products, which arises by rapid equilibration to a single organolithium. However, transmetallation of the 64:36 mixture of **12b** and **12a** behaved differently. Transmetallation was incomplete even after 90 min at −78°C, and the minor diastereoisomer, **12a** (E = $SnBu_3$), transmetallated faster than the major diastereoisomer, leaving a 73:27 mixture of **12b** and **12a** (E = $SnBu_3$) after this time. Methylation of the organolithium formed by transmetallation gave, in 15% yield, an 88:12 mixture of **12a** and **12b** (E = Me). Tin–lithium exchange of α-heterosubstituted stannanes occurs with reliable retention of stereochemistry,[16] so formation of the same diastereoisomer of **12** (E = Me) by lithiation of **9** and by transmetallation of the *minor* diastereoisomer of the stannane (E = $SnBu_3$) suggests that both organolithiums are the same and therefore that their stannylation proceeds principally with inversion of stereochemistry.[17] The widely varying stereospecificity of electrophilic substitution reactions of α-heterosubstituted benzyllithiums[18] makes us wary of proposing definitive retentive or invertive pathways for other electrophiles. We know for certain the stereochemistry of the final products **12a** (E = Me) and **12a** (E = CO_2Me), and MeI and $ClCO_2Me$ must therefore react with the same stereospecificity (whether retention or inversion) as each other. For simplicity we have inferred that both substitute retentively, but alkylation is commonly invertive,[17] and this assignment must be taken purely tentatively. Mixtures of diastereoisomers formed by allylation and benzylation may arise from the intervention of radical intermediates.[19,20]

In summary, the lithiation and alkylation of α-methyl-*N*,*N*-dibenzylamine derivatives provides the best route to derivatives of *meso* bis-(α-methylbenzyl)amine **2** and an alternative route to derivatives of phenylglycine. *N*-Acyl-α-methyl-*N*,*N*-dibenzylamines also provide a convenient platform from which to investigate the stereochemistry in the reactions of amino-substituted benzyllithiums.

Acknowledgements

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