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N to C Aryl Migration in Lithiated Carbamates: α-Arylation of Benzylic Alcohols

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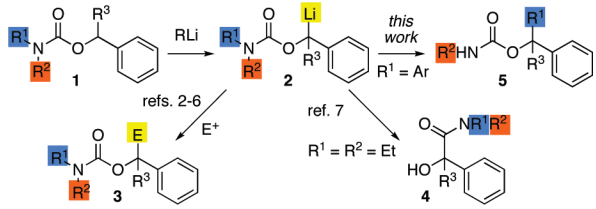
Lithiation α to oxygen[1] of carbamates such as **1** ($R^1 = R^2 =$ *i*-Pr)[2] and its nonbenzylic counterparts[3] generates a series of d^1 reagents **2** that may be alkylated or acylated to give **3**, providing a strategically uncommon route to secondary and tertiary alcohols.[4] In many cases, the intermediate organolithiums **2** may be made in enantiomerically pure form by use of (−)-sparteine-complexed organolithiums;[5] reliable retentive or invertive electrophilic substitution[4,6] permits **3** to be made enantioselectively. Less hindered carbamates **2** (for example, $R^1 = R^2 =$ Et), however, are too unstable on standing at −78 °C: rearrangement by 1,2-acyl transfer from O to C provides α-hydroxyamides **4** (Scheme 1).[7]

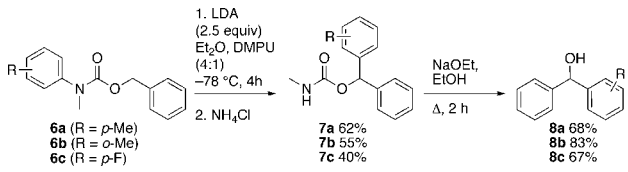
Scheme 1. Versatile Reactivity of Lithiated Carbamates



In this paper, we report our discovery of a third mode of reactivity, displayed by carbamates carrying an *N*-aryl substituent (R^1 = Ar in Scheme 1): upon lithiation, the *N*-aryl group is transferred cleanly from N to C. An arylation of the carbamate results, providing a route to α,α-arylated secondary or tertiary alcohols. We also report theoretical studies that illuminate the mechanism of the attack on the aromatic ring, a significantly lower energy pathway than the expected[7] 1,2-acyl transfer.

O-Benzyl carbamate **6a** was treated with LDA (2.5 equiv) in 4:1 Et_2O/DMPU[8] at −78 °C. The solution became orange-red, and upon workup, a product **7a** in which the aryl ring had migrated from N to C was obtained (Scheme 2). Other *O*-benzyl-*N*-aryl carbamates **6b** and **6c** rearranged in a similar manner, providing carbamate derivatives **7b** and **7c** of diarylmethanols. The alcohols **8a**−**c**[9] were returned by simple treatment of the carbamates with sodium ethoxide in ethanol.

Scheme 2. Diarylmethanols by Aryl Transfer



A series of related carbamates **9** was made from α-methylated benzylic alcohols and subjected to lithiation in a similar way, either with LDA in Et_2O/DMPU or *s*-BuLi in THF/DMPU. Under either set of conditions, comparable 1,4-aryl transfers from N to C took place, and the arylated carbamate products **10** were isolated in good to excellent yields (Scheme 3 and Table 1). No competing 1,2-acyl shift was observed.

Scheme 3. Aryl Transfer in Lithiated Carbamates

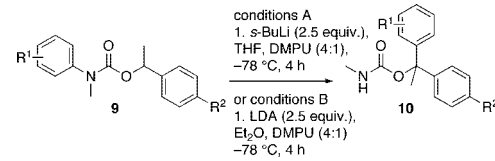


Table 1. Rearrangements of Carbamates **9**

entry	s. m.	R^1	R^2	conds.	**10**, yield (%)
1	**9a**	H	H	A	**10a**, 75
2	**9b**	*p*-Me	H	B	**10b**, 84
3	**9c**	*o*-Me	H	B	**10c**, 72
4	**9d**	*o*-*i*-Pr	H	B	**10d**, 67
5	**9e**	*p*-OMe	H	A	**10e**, 68
6	**9f**	*p*-Cl	H	B	**10f**, 56
8	**9g**	2,3-benzo	H	A	**10g**, 85
7	**9h**	3,4-benzo	H	A	**10h**, 57
8	**9i**	H	*p*-Cl	B	**10f**, 90
9	**9j**	*p*-Me	*p*-Cl	B	**10j**, 82
10	**9k**	*p*-OMe	*p*-Cl	A	**10k**, 68
11	**9l**	2,3-benzo	*p*-Cl	A	**10l**, 67

α,α-Diaryl ethanols are valuable compounds in enantiomerically pure form.[10] For example, (*R*)-**11**, which has been made by a range of different enantioselective methods,[4,11] is an intermediate in the synthesis of the antihistamine agent clemastine.[12] However, attempts to make **10** enantioselectively by stereospecific rearrangement of **9** were apparently hampered by the decreased configurational stability of O-substituted benzyllithiums **2** in strongly lithium-coordinating solvents.[6,13] When (*R*)-**9g** was used as starting material, for example, **10g** was produced in racemic form using conditions A. Likewise, **10f** was formed as a racemate from (*S*)-**9i** with conditions B.

Replacing the lithium-coordinating additives THF and DMPU led to a significant improvement in the product er, presumably because these additives otherwise enhance the rate of organolithium racemization.[6] When (*R*)-**9g** and (*S*)-**9i** were lithiated in Et_2O with *s*-BuLi and LDA, respectively, substantial enantiomeric enrichment was preserved: (*S*)-**10g** was returned in 75:25 er and (*S*)-**10f** in 85:15 er (from a starting material of 94:6 er), respectively (Scheme 4). However, in the absence of DMPU, the rearrangement was slower, and lower yields of rearranged products were obtained. Enantiomerically enriched (*S*)-**10f** was converted into alcohol (+)-(*S*)-**11**[4,11] by refluxing with sodium ethoxide in ethanol. Comparison with published data[4,14] for optical and chromatographic properties of (+)-(*S*)-**11** confirmed its absolute stereochemistry and

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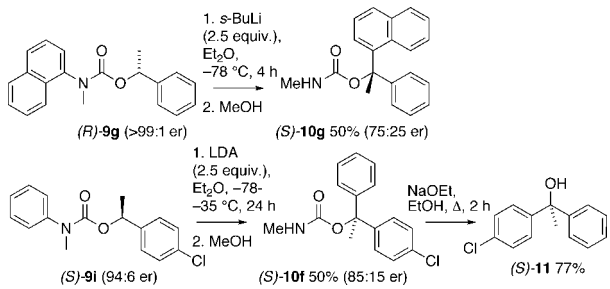
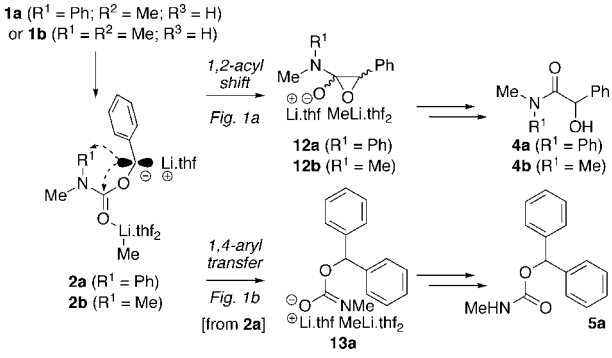
Scheme 4. Enantioselectivity in the Rearrangement



showed that rearrangement proceeded with inversion at the lithium-bearing center.

To illuminate the mechanism of the rearrangement and the selectivity with regard to the competition between 1,2-acyl shift and 1,4-aryl transfer, the stationary structures involved in the conversion of the organolithium intermediate **2** to both **4** and **5** with inversion at the carbanion center (Scheme 5) were determined using density functional theory (DFT) calculations.[15] A simple carbamate **1a** with R^1 = Ph, R^2 = Me, and R^3 = H was chosen as the substrate. The anionic intermediate **2a** was coordinated with two Li^+ cations [one as an alkyllithium (methyllithium, for simplicity) to represent the excess RLi] and three THF solvent molecules, and a continuum description of the bulk solvent was used.

Scheme 5. Mechanism and Selectivity: 1,4-Aryl versus 1,2-Acyl Transfer



The structures identified for the transition states from **2a** en route to **4a** (1,2-acyl shift) and **5a** (1,4-aryl transfer) are shown in Figure 1a,b. The calculated free energy barrier for the attack on the aromatic ring (3.6 kJ mol^{-1}) is considerably lower (by 14.4 kJ mol^{-1}) than that for attack on the carbonyl group (18.0 kJ mol^{-1}). For a 1,2-acyl shift in the *N,N*-dimethyl carbamate **1b**, the corresponding barrier (22.7 kJ mol^{-1}) is close to the value for the conversion of **2a**, showing that the *N*-phenyl group favors aryl transfer simply by opening up an alternative pathway rather than by disfavoring the 1,2-acyl shift.

Rearrangement yields were best in the presence of DMPU and excess alkyllithium, and the calculations illuminate the possible role of these additives. We find that during the course of the reaction, one Li^+ ion remains close to the carbonyl oxygen atom while a second lithium ion migrates from the carbanion center to the adjacent oxygen atom (Figure 1), thus freeing the carbanion for nucleophilic attack. We also find that in the absence of the THF, Li^+, and CH_3^- species, the conversion of **2a** leading to **5a** is calculated to proceed without a barrier, showing the stabilization of the reactant **2a** and suggesting that the role of DMPU may be to solvate the Li^+ cation and generate a reactive ion pair.[7]

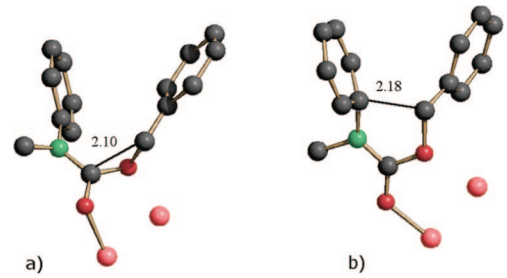


Figure 1. Transition structures for (a) 1,2-acyl transfer and (b) 1,4-aryl transfer. Coordinated THF solvent molecules and the Me^- counterion have been omitted for clarity. Interatomic distances are given in angstroms.

We are currently working to broaden the scope of this new reaction to other *N*-aryl-substituted carbamate analogues.

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Supporting Information Available: Full experimental procedures and characterization data for compounds reported in the paper, together with details of computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See the Supporting Information for evidence of the stereochemical assignment of (+)-(*S*)-**11** and hence the invertive nature of the rearrangement. Electrophilic quenching of lithiated benzylic carbamates may proceed with either retention or inversion; see ref 6 and: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
(15) DFT calculations were carried out at the B3LYP/6-31++G** level, with thermodynamic corrections (including zero-point effects) at the B3LYP/6-31G level (see the Supporting Information for details.

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