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# Lithium Choreography: Intramolecular Arylations of Carbamate-Stabilised Carbanions and Their Mechanisms Probed by In Situ IR Spectroscopy and DFT Calculations

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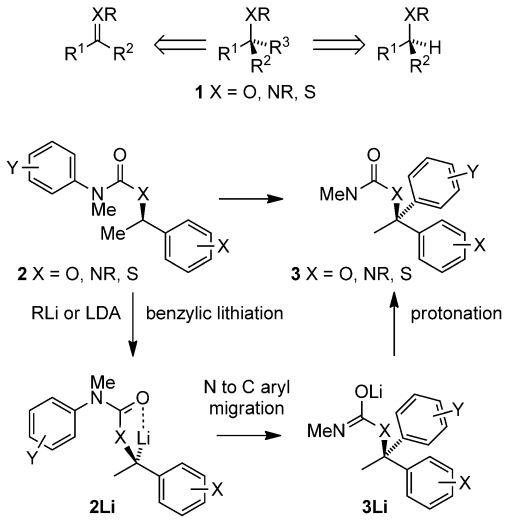
**Abstract:** Deprotonation of *O*-allyl, *O*-propargyl or *O*-benzyl carbamates in the presence of a lithium counterion leads to carbamate-stabilised organolithium compounds that may be quenched with electrophiles. We now report that when the allylic, propargylic or benzylic carbamate bears an *N*-aryl substituent, an aryl migration takes place, leading to stereochemical inversion and C-arylation of the carbamate α to oxygen. The aryl migration is an intramolecular $S_NAr$ reaction, despite the lack of anion-stabilising aryl substituents. Our in situ IR studies reveal a number of intermediates along the rearrangement pathway, including a "pre-lithiation complex," the deprotonated carbamate, the rearranged anion, and the final arylated carbamate. No evidence was obtained for a dearomatised intermediate during the aryl migration. DFT calculations predict that during the reaction the solvated Li cation moves from the carbanion centre, thus freeing its lone pair for nucleophilic attack on the remote phenyl ring. This charge separation leads to several alternative conformations. The one having $Li^+$ bound to the carbamate oxygen gives rise to the lowest-energy transition structure, and also leads to inversion of the configuration. In agreement with the IR studies, the DFT calculations fail to locate a dearomatised intermediate.

**Keywords:** carbamates · density functional calculations · IR spectroscopy · lithium · organolithium · reaction mechanisms · rearrangement

## Introduction

The synthesis of compounds **1**, containing quaternary stereogenic centres bearing a heteroatom, is a challenge that has been met in a number of ways,[1–4] most of which fall into two classes: 1) the enantioselective addition of a nucleophile to a prochiral π system (a ketone or imine, for example),[1] or 2) the stereospecific elaboration of an existing tertiary stereogenic centre (Scheme 1).[4] Both methods offer advantages, with the latter allowing the formation of stereogenic centres in an enantiomerically pure fashion even when the centre carries groups that are sterically and electronically similar. We have shown that benzylic carbamates,[5,6] ureas[7–9] and thiocarbamates[10] **2**, containing *N*-aryl substituents, undergo an N to C aryl migration reaction, allowing introduction of an aryl substituent α to the benzylic heteroatom (Scheme 1). With derivatives of enantiomerically pure secondary alcohols or thiols, or amines with secondary substituents, the migration may be stereospecific, generating a product **3** containing a new quaternary stereogenic centre bearing an acylated O, N or S substituent. The stereospecificity is dependent on the configurational stability of the in-




Scheme 1. Quaternary centres carrying heteroatoms: aryl migration in benzyllithium compounds.

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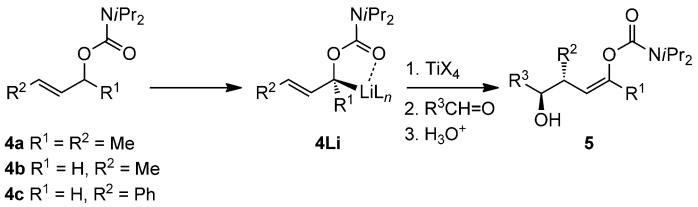
termediate organolithium **2Li** over the timescale of the rearrangement, and is high for ureas, slightly lower for thiocarbamates and significantly lower for carbamates. Deprotection in basic[6] or neutral conditions[8] reveals an α-arylated amine,[2] alcohol or thiol[3] product. Aggarwal et al. have reported[4] a method for the synthesis of tertiary alcohols which also proceeds through lithiation of a benzylic carbamate. Trapping with a borane or a boronic ester proceeds with stereochemical retention or inversion, and a concomitant 1,2-shift, entailing departure of the carbamate, leads to formation of a chiral borane or boronate that may be oxidised to a tertiary alcohol.

Prior to this work, it was well established that not only benzylic[11] but also allylic and propargylic carbamates may be deprotonated to form synthetically versatile organolithium compounds of defined stereochemistry.[12] Hoppe et al. used α-metallated 2-alkenyl *N*,*N*-diisopropylcarbamates **4Li** as homoenolate equivalents in regio- and stereospecific reactions with aldehydes and ketones (Scheme 2).[13] Enantioenriched (α-lithio-2-alkenyl)-carbamates derived from secondary carbamates, such as (*E*)-2-pentenyl *N*,*N*-diisopropylcarbamate (**4a**), are configurationally stable below −70 °C in non-polar solvents. They can be generated either by deprotonation of the optically active precursors by *n*-butyllithium/tetramethylethylenediamine (TMEDA) in diethyl ether/hexane[14] or by kinetic resolution of racemic precursors, deprotonating with *sec*-butyllithium/(−)-sparteine in pentane. The allyllithium is formed with greater than 80% *ee*, as estimated from trapping experiments.[15]

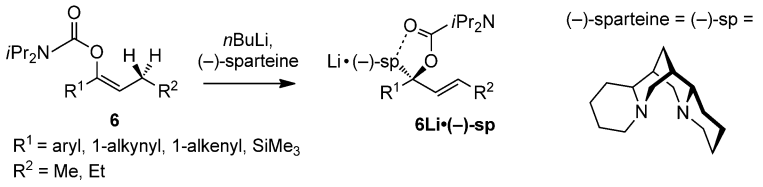



Scheme 2. Allylic carbamates in homoaldol reactions.

In contrast, (α-lithio-2-alkenyl)carbamates **4Li** derived from carbamate derivatives of primary alcohols, such as (*E*)-2-butenyl *N*,*N*-diisopropylcarbamate (**4b**)[16] or (*E*)-cinnamyl *N*,*N*-diisopropylcarbamate (**4c**),[17] turn out to be configurationally unstable in solution with butyllithium/(−)-sparteine even at −78 °C. In the case of (*E*)-2-butenyl *N*,*N*-diisopropylcarbamate (**4b**), however, the sparteine complex crystallises from a pentane/cyclohexane solution with concomitant dynamic kinetic resolution, resulting in up to 96:4 d.r. in the solid. Reaction of the solid with Ti(O*i*Pr)$_4$ proceeds with configurational inversion to give the allyltitanium intermediate, which is stable in solution and adds to aldehydes and ketones to form homoaldol products **5** with >95:5 d.r.[16] Deprotonation of (*E*)-cinnamyl *N*,*N*-diisopropylcarbamate (**4c**) with *n*-butyllithium/(−)-sparteine in toluene shows that the cinnamyllithium **4cLi** compound formed upon deprotonation epimerises within thirty minutes at −78 °C to a thermodynamically controlled ratio of diastereoisomeric allyllithium–(−)sparteine complexes. Reactions with several electrophiles proceed regio- and stereospecifically at the α- or γ-position but at different rates for the two diastereomers, leading to a decrease in enantioselectivity compared to the diastereomeric ratio of the complexes.[17a] Lithiation of cinnamyl carbamates and their 1-naphthyl analogues in the presence of chiral bisoxazoline (BOX) ligands results in a greater discrimination between the diastereoisomers than with (−)-sparteine, and gives enantioenriched substitution products with *ee* values up to 94%.[17b]

(*Z*)-1-Alken-1-yl *N*,*N*-diisopropylcarbamates **6** bearing an anion-stabilising group in the 1-position are deprotonated by *n*-butyllithium/(−)-sparteine with a high degree of selectivity between the enantiotopic protons at the γ-position to form allyllithium intermediates **6Li** that are configurationally stable at −70 °C (Scheme 3). These combine with ketones and aldehydes with high regio- and stereoselectivities (up to 97% *ee*), allowing a simple and efficient approach to enantiomerically enriched homoenolate reagents starting from achiral precursors.[18]

In the alkyne series, enantiomerically enriched, configurationally stable propargyllithium compounds may be produced by deprotonation of enantiomerically pure secondary 2-alkynyl *N*,*N*-diisopropylcarbamates with *n*-butyllithium/TMEDA in hexane at −78 °C.[19] Deprotonation of primary 2-alkynyl *N*,*N*-diisopropylcarbamates by *n*-butyllithium/(−)-sparteine in toluene at −78 °C and trapping the intermediate ion pairs by carboxylation or silylation leads to slightly enantioenriched products. However, when the deprotonation is carried out in pentane, dynamic resolution of the lithium–(−)-sparteine complexes by selective crystallisation gives much higher levels of enantioselectivity (up to 96:4 e.r.).[20]

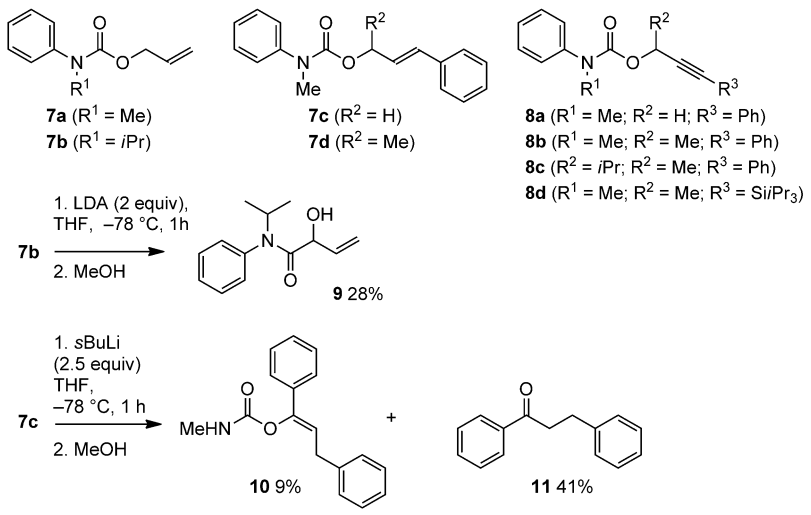



Scheme 3. Enantiotope-differentiating γ-deprotonation of 1-alkenyl carbamates.

Lithiated allylic and propargylic carbamates have thus proved their worth in stereoselective synthesis in which the organolithium is trapped by an electrophile such as a carbonyl compound or alkylating agent. However, there are currently no methods allowing the stereoselective arylation of lithiated allyl or propargyl carbamates. We therefore set

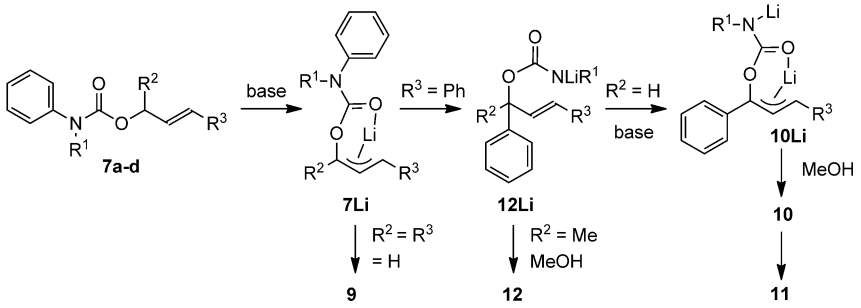
out to explore the potential of aryl migration within the lithiated carbamate as a means to achieve this aim, bearing in mind that aryl migration in lithiated ureas is an effective method for the synthesis of hindered benzylic amines.[2,7] In this paper, we describe the scope and limitations of the aryl migration reactions as a means of making tertiary allylic or propargylic alcohols. We also describe spectroscopic (in situ IR) and computational (DFT) investigations into the mechanism of the reaction, including its stereospecificity for inversion.




Scheme 4. Aryl migration in lithiated allyl carbamates: preliminary experiments

## Results and Discussion

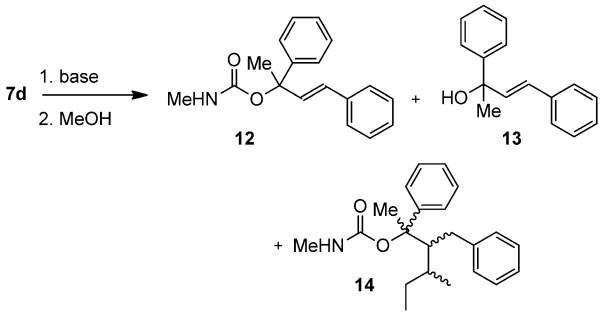
**Scope of the rearrangement**: In preliminary experiments to assess the reactivity of lithiated *O*-allyl-*N*-aryl carbamates towards rearrangement, we treated a series of substituted *O*-allyl-*N*-aryl carbamates **7**[21] with a base (Scheme 4). The simplest member of the set, **7a** (*N*-methyl aniline protected as its *N*-allyloxycarbonyl (*N*-Alloc) derivative), decomposed under basic conditions, but **7b** underwent lithiation followed by a 1,2-acyl shift from nitrogen to carbon to give compound **9**—a known reaction of lithiated carbamates,[22] and one we have previously observed as a side reaction in N to C aryl migrations.[23] More encouraging results were obtained from *O*-cinnamyl carbamate **7c** on treatment with *s*BuLi (2.5 equiv) in THF at −78 °C. After 1 h, the principal product of the reaction (41 % yield) was the aryl ketone **11**, a compound that can only arise by migration of the *N*-phenyl ring from N to C, and a minor product was enol carbamate **10**, from which **11** can be derived by hydrolysis.




Scheme 5. Proposed pathway to rearrangement products **9**–**12**. Solvation of the lithium cation is assumed but not explicitly shown.

A plausible pathway from **7c** to **10**, and hence **11**, is shown in Scheme 5. Deprotonation of **7** to give the allyllithium **7Li** is followed by aryl migration to yield **12Li**. A second deprotonation gives **10Li**, and γ-reprotonation during the workup yields the vinyl carbamate **10**.

To capture the initial product of rearrangement, **12Li**, without the complicating features of the second deprotonation, we replaced the cinnamyl derivative (**7c**) with its α-methylated analogue **7d**. On deprotonation with *s*BuLi (Scheme 6), the principal isolated product **14** (23 %) contained a *sec*-butyl group (Table 1, entry 1). This compound




Scheme 6. Rearrangement of an α-methylated allyl carbamate.

presumably arises from aryl migration to give **12** followed by carbolithiation[24] of the styrenic double bond. Traces of a second product **13**, formed in 6 % yield, suggested rearrangement to **12** (Scheme 5), followed by loss of the carbamate.

Deprotonation of **7d** with lithium diisoproylamide (LDA) in THF and quenching with MeOH gave, after 30 min, a compound identified as **12** in the NMR spectrum of the crude reaction mixture (Table 1, entry 2). However, this material proved extremely unstable under the conditions re-

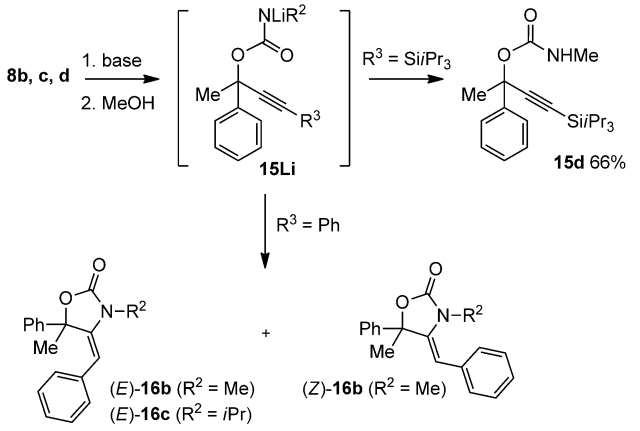
Table 1. Choice of base for rearrangement of allyl and propargyl carbamates.

| Entry | S.M. | Base | Product, yield [%] | e.r.[a] |
|---|---|---|---|---|
| 1 | **7d** | *s*BuLi (2.5 equiv), THF, −78 °C, 1 h | **13**, 6; **14**, 23 | – |
| 2 | **7d** | LDA (2 equiv), THF, −78 °C, 30 min | **12**[b] | – |
| 3 | **7d** or (*R*)-**7d** | LDA (2 equiv), THF, −78 °C, 30 min; then *t*BuONO (6 equiv), RT, 16 h | **13**, 68 | 50:50 |
| 4 | (*R*)-**7d** | LDA (2 equiv), $Et_2O$, −78 °C, 2 h; then *t*BuONO (6 equiv), RT, 16 h | (−)-(*S*)-**13**[c] | 54:46[d] |
| 5 | (*R*)-**7d** | LDA (2 equiv), $Et_2O$, (−)-sparteine, −45 °C, 2 h; then *t*BuONO (6 equiv), RT, 16 h | (−)-(*S*)-**13**[c] | 62:38 |
| 6 | **8b** or (*S*)-**8b** | LDA (2 equiv), THF, −78 °C, 15 min | (*E*)-**16b**, 45 | 50:50 |
| 7 | **8c** or (*S*)-**8c** | LDA (2 equiv), THF, −78 °C, 15 min | (*E*)-**16c**, 70 | 50:50 |
| 8 | **8b** | LiHMDS (2 equiv), THF, 0 °C, 15 min | (*E*)-**16b**, 14; (*Z*)-**16b**, 31 | – |
| 9 | **8b** | NaHMDS (2 equiv), THF, 0 °C, 15 min | (*E*)-**16b**, 7; (*Z*)-**16b**, 44 | – |
| 10 | **8b** | KHMDS (2 equiv), THF, 0 °C, 15 min | (*E*)-**16b**, 16; (*Z*)-**16b**, 16 | – |
| 11 | **8d** | LDA (2.5 equiv), THF, DMPU, −78 °C, 1 h | **15d**, 66 | – |

[a] The e.r. was determined from the crude reaction mixture. [b] Observed in the crude reaction mixture. [c] Configuration assigned by comparison with a reported optical rotation: $[\alpha]_D^{25} = -1.5$ ($c = 1.0$ in $CHCl_3$); literature value $[\alpha]_D^{20} = -5.33$ ($c = 0.6$ in $Et_2O$] (see ref. [26]). [d] The remaining starting material was recovered with 77:23 e.r. HMDS = hexamethyldisilazide, DMPU = 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one.

quired for purification, presumably due to the ready formation of a highly stabilised cation under acidic conditions. By adding instead *tert*-butyl nitrite to form an *N*-nitroso derivative in situ[25] and stirring the resulting basic reaction mixture for 24 h at room temperature, the alcohol **13** could be obtained in 68% yield (Table 1, entry 3). Under these conditions the aryl migration clearly takes place cleanly and in good yield, the applicability of the reaction being limited only by the instability of the product.

The related propargyl carbamates behaved in a comparable manner. As with **7a**, primary *O*-propargylcarbamate **8a**, on treatment with base, produced products of attack directly on the carbamate C=O group. However, with the α-methylated analogues of this compound **8b–d**, treatment with base led to migration of the aryl ring from N to C (Scheme 7),




Scheme 7. Rearrangement of *O*-propargylcarbamates.

and in the case of **8d** the rearranged carbamate **15** was isolated in 66% yield. With the phenyl-substituted alkynes **8b** and **8c**, the migration was followed by cyclisation of the resulting carbamate anion **15Li** onto the triple bond[27] to yield the benzylidene oxazolidinones (*E*)- and (*Z*)-**16** (Table 1, entries 6–10) in a ratio dependent upon the base used in the cyclisation. X-ray crystallography confirmed the

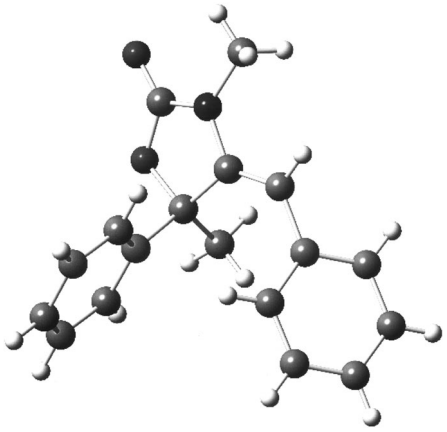
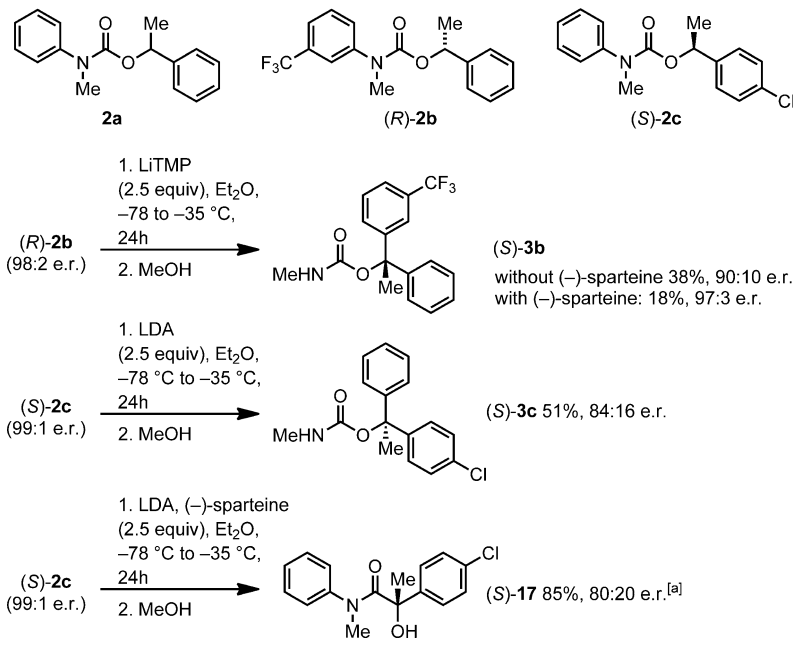


Figure 1. X-ray crystal structure of (*E*)-**16b**.

structure of the cyclised product (*E*)-**16b** (Figure 1). The cyclisation, although interesting, detracts from the possible utility of the rearrangement. Nevertheless, the formation of these compounds also indicates that the aryl migration can be initiated by organometallic intermediates of potassium and sodium, something not observed previously.

By starting with enantiomerically pure **7d**, we hoped to be able to form the allyllithium compound **7dLi** as a single enantiomer that would rearrange to **12dLi** faster than it can racemise. Enantiomerically enriched benzylcarbamates may be lithiated and rearranged stereospecifically, provided conditions are carefully chosen,[6] and carbamates closely related to **7d** have some degree of configurational stability.[14,28] Compound (*R*)-**7d** was made by kinetic resolution[29] of its allylic alcohol precursor. Treatment with LDA in THF under the conditions used for the reaction in Scheme 6, however, returned the racemic product (Table 1, entry 3). Since rearrangements in less coordinating solvents tend to return higher enantiomeric excesses,[6,10] the reaction was repeated in diethyl ether. However, this reaction did not reach completion in 2 h, and gave a product with a low enantiomeric excess (Table 1, entry 4). Tellingly, the recovered starting material was also partially racemised, suggesting that the




Scheme 8. Effect of (−)-sparteine on the rearrangement of lithiated benzylcarbamates. [a] The absolute configuration of (*S*)-**17** remains unassigned.

lithiated intermediate is not configurationally stable under the reaction conditions. Diamines such as (−)-sparteine or TMEDA may affect the rate at which organolithium compounds racemise,[30] and indeed adding either (−)-sparteine or TMEDA (1 equiv) to the rearrangement in $Et_2O$ resulted in a product retaining some degree of enantiomeric enrichment (Table 1, entry 5). The maximum achievable e.r. was little more than 60:40, but the sign of the optical rotation of the product (−)-(*S*)-**13** was consistent with the literature value for this compound[26] and confirmed the absolute configuration of the major enantiomer.[31] It appears therefore that the rearrangement of allyl carbamates, like that of benzyl carbamates,[5,6] proceeds with inversion of configuration. This is in stark contrast with the related rearrangements of ureas[7,32] (including allyl ureas[23]) and thiocarbamates.[10]

Similarly, enantiomerically enriched *O*-propargyl carbamates (*S*)-**8b** and (*S*)-**8c** were made by reduction of 4-phenylbut-3-yn-2-one by using the method reported by Noyori and co-workers.[33] As expected, in THF at −78 °C, the rearrangement/cyclisation of (*S*)-**8b** or (*S*)-**8c** with LDA gave only racemic product (Table 1, entries 6 and 7). Replacing THF with $Et_2O$ diverted the course of the reaction of **8b** towards attack directly on the carbamate C=O group, whereas, with **8c**, $Et_2O$ completely shut down the reaction. At various temperatures, with or without addition of (−)-sparteine, decay of the *ee* of the starting material, by racemisation of its lithium derivative, was observed.

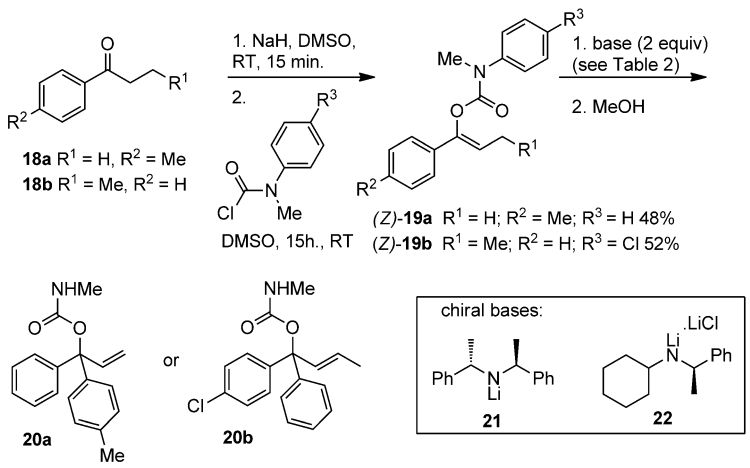
The use of (−)-sparteine as a means of reducing the rate of racemisation[30] relative to the rate of rearrangement was explored as a way of improving the results obtained from the rearrangements of benzyl carbamates **2** described previously (Scheme 8).[5] Addition of (−)-sparteine to the rearrangement of (*R*)-**2b** improved the e.r. of the product, (*S*)-**3b**, from 90:10 to 97:3, but at the expense of the yield, whereas addition of (−)-sparteine to the less reactive (*S*)-**2c** induced a remarkable change in the mechanism of the reaction, which produced the 2-hydroxyamide (*S*)-**17**, by a 1,2-acyl shift, in 80:20 e.r., instead of the aryl migration product (*S*)-**3c**, generated in the absence of (−)-sparteine.[34]

*N*- or *O*-Substituted allyllithium compounds may be formed either by α-deprotonation of an allylamine/allyl alcohol derivative or alternatively by γ-deprotonation of an enamine/enol derivative.[28] The advantage of the latter method is the lack of chirality in the starting material, which provides yet another mechanistic possibility for carrying out an enantioselective rearrangement—asymmetric deprotonation. We had previously shown that asymmetric γ-deprotonation of an *N*-carbamoyl enamine (an *N*-vinyl urea) with chiral lithium amides generates *N*-substituted allyllithium compounds enantioselectively.[23] The corresponding *N*-aryl-(*Z*)-enol carbamates **19** were made by the method reported by Feringa et al.:[35] the sodium enolates of the ketones **18** were *O*-acylated by addition of the carbamoyl chloride derivatives of *N*-methyl aniline or *N*-methyl-4-chloroaniline (Scheme 9).

Treatment of the *O*-vinylcarbamates **19** with LDA (2 equiv) in THF gave the rearranged carbamates **20**, derivatives of tertiary doubly benzylic alcohols, in excellent yield (Scheme 9), indicating that the reactivity towards migration of the aryl ring from N to C of lithiated *O*-allyl, *O*-benzyl and *O*-vinyl carbamates bearing *N*-aryl groups provides a valuable method for arylating an organolithium centre adjacent to an oxygen atom from very easily made substrates. Replacing LDA with chiral analogues **21** or **22**[23] led to a slower reaction, and levels of enantiomeric enrichment were relatively poor, reaching a maximum of 68:32 (Table 2). Again it seems likely that racemisation competes with rearrangement, and no further enantioselective reactions were pursued with these compounds.

**Identification of reaction intermediates by in situ infrared spectroscopy**: The presence of the carbonyl group makes carbamates particularly suitable for mechanistic studies by in situ IR spectroscopy. Recently, O'Brien et al.[36] reported that the lithiation of *N*-*tert*-butoxycarbonyl (*N*-Boc) piperidine with *s*BuLi/TMEDA, (−)-sparteine or (+)-sparteine could be followed by in situ infrared spectroscopy. A "pre-




Scheme 9. γ-Deprotonation-mediated N to C aryl transfer in enolcarbamates.

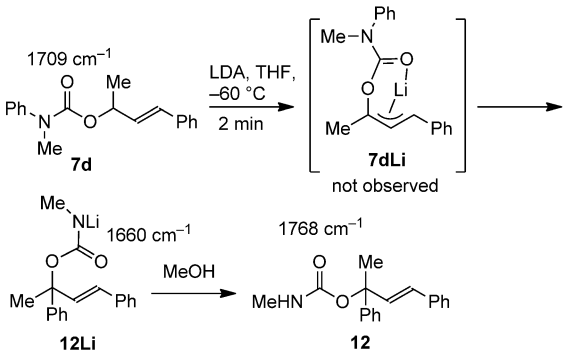
Table 2. Lithiation and rearrangement of (*Z*)-**19a** and (*Z*)-**19b**.

| Starting material | Base | *T* [°C] | *t* [h] | Product | Yield [%] | e.r. |
|---|---|---|---|---|---|---|
| (*Z*)-**19a** | LDA[a] | −78 | 1 | **20a** | 80 | – |
| (*Z*)-**19b** | LDA[a] | −45 | 1 | **20b** | 80 | – |
| (*Z*)-**19a** | **21**[b] | −78 | 3 | **20a** | 28[d] | 68:32 |
| (*Z*)-**19a** | **22**[c] | −78 | 5 | **20a** | 72 | 56:44 |
| (*Z*)-**19a** | **21**[b] | −60 | 3 | **20a** | 50[e] | 54:46 |
| (*Z*)-**19b** | **21**[b] | −78 | 5 | **20b** | 18[d] | 52:48 |
| (*Z*)-**19b** | **21**[b] | −60 | 3 | **20b** | 62 | 52:48 |

[a] In THF. [b] From the amine and *n*BuLi. [c] From the amine hydrochloride and 2×*n*BuLi. [d] Starting material remaining. [e] Formation of a side-product.

lithiated complex" ($\tilde{\nu}_{C=O}=1675\ cm^{-1}$) between the substrate and the lithiating agent was observed in *tert*-butyl methyl ether (TBME) at −78 °C prior to formation of the lithiated piperidine ($\tilde{\nu}_{C=O}=1644\ cm^{-1}$).[36] Beak et al. also monitored the lithiation of an *N*-Boc allylamine through in situ IR spectroscopy with *n*BuLi/(−)-sparteine in toluene at −73 °C,[37] reporting a similar reaction pathway involving a pre-lithiated complex with an IR peak at $\tilde{\nu}=1675\ cm^{-1}$ and a lithiated complex that appears at $\tilde{\nu}=1640\ cm^{-1}$. Addition of *n*BuLi to *N*-Boc allylamine generated a stable carbamate–*n*BuLi complex with an IR peak at $\tilde{\nu}=1675\ cm^{-1}$ and addition of (−)-sparteine led to deprotonation, as seen by the appearance of the peak at $\tilde{\nu}=1640\ cm^{-1}$. Our own previous studies in this area initially explored the rearrangements of ureas in THF by NMR spectroscopy[38a] and by in situ IR spectroscopy,[38] and failed to find evidence of either a pre-lithiation complex or of the presence of a postulated dearomatised intermediate with a benzenoid ring migrating (though a dearomatised intermediate was observed, and indeed trapped, with a migrating naphthyl ring). However, in THF, the rearrangement is fast. We recently found[38b] that a pre-lithiation complex can be detected by in situ IR spectroscopy during a rearrangement involving vinyl migration, but only in $Et_2O$ or toluene. Again, no intermediate could be found between the lithiated starting material and the rearranged product. To explore the pathway from starting material to product in lithiated carbamates, we therefore undertook detailed in situ IR studies, in a range of solvents, of the rearrangements of representative allylic, vinylic and benzylic carbamates, **7d**, **19b** and **2c**.

In a flask equipped with the probe of a React IR machine, **7d** was treated with LDA (1.5 equiv) at −60 °C in THF (Scheme 10). On addition of LDA, the C=O stretching frequency of $\tilde{\nu}=1709\ cm^{-1}$, corresponding to the starting carbamate **7d**, was replaced over 2 min by a band at $\tilde{\nu}=1660\ cm^{-1}$, which persisted until, after 45 min, the reaction was quenched with methanol. At this point a peak at $\tilde{\nu}=1768\ cm^{-1}$ appeared, which corresponds to the product carbamate **12** (Figure 2). In this reaction, and under these conditions, we saw no evidence for any other intermediates, and we assume that the band at $\tilde{\nu}=1660\ cm^{-1}$ corresponds to the product anion **12Li**, which forms by instantaneous rearrangement of the lithium derivative **7dLi**.




Scheme 10. Proposed intermediates in the rearrangement of **7d**. Solvation of the lithium cation is assumed but not explicitly shown.

The rearrangement of **19b** (Scheme 11) provided more detail about the mechanistic pathway, presumably because the allyl anion generated by deprotonation is more stable than that formed from **7d**. Immediately upon addition of LDA to **19b** in THF at −60 °C, a new band at $\tilde{\nu}=1578\ cm^{-1}$ appeared and lasted for only a few minutes, before giving way to a band at $\tilde{\nu}=1649\ cm^{-1}$ (Figure 3). This band, which corresponds to the band at $\tilde{\nu}=1660\ cm^{-1}$ in Figure 2, persisted until the reaction is quenched, which generated the product peak at $\tilde{\nu}=1735\ cm^{-1}$. The band at $\tilde{\nu}=1649\ cm^{-1}$ is again presumably that corresponding to the product anion **20bLi**, with the band at $\tilde{\nu}=1578\ cm^{-1}$ presumably arising from the lithiated starting material **19bLi**.

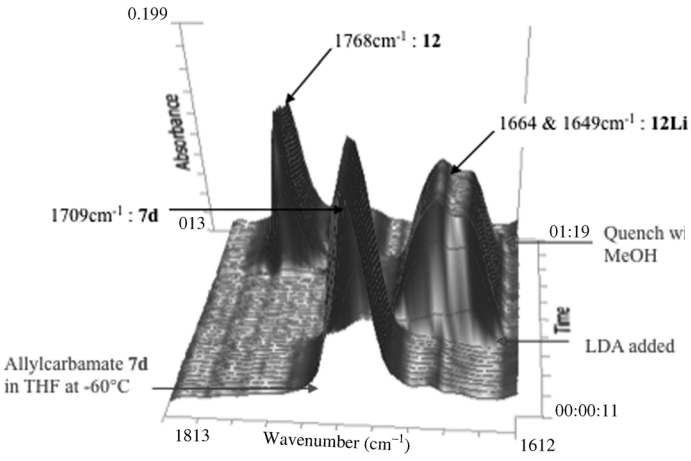
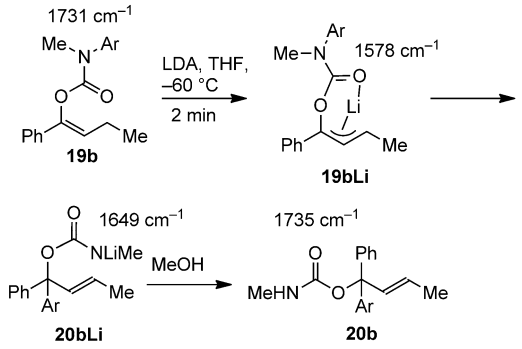



Figure 2. The in situ IR spectra of the rearrangement of **7d** during the reaction using LDA in THF at −60 °C (a three-dimensional plot of absorbance versus wavenumber versus time).




Scheme 11. Intermediates detected in the rearrangement of **19b** (Ar = *p*-$ClC_6H_4$). Solvation of the lithium cation is assumed but not explicitly shown.

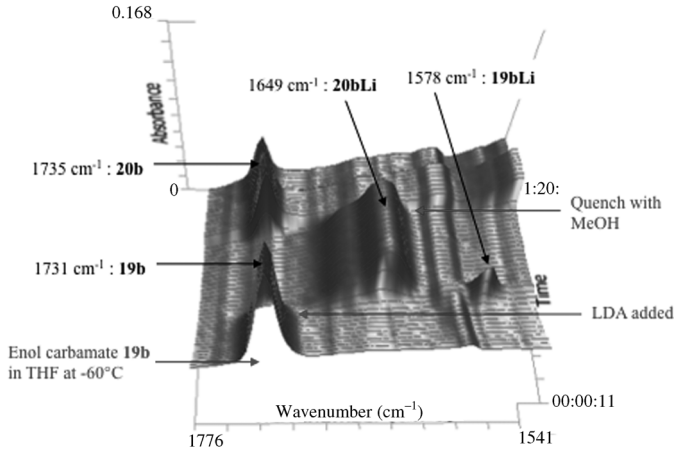
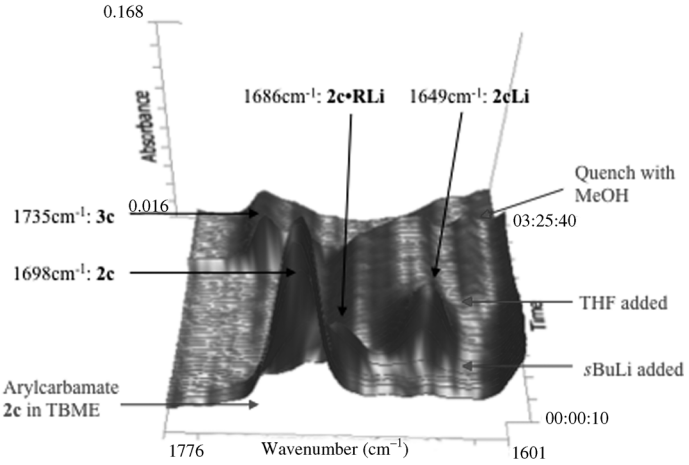



Figure 3. A three-dimensional infrared profile for the rearrangement of **19b** by using LDA in THF at −60 °C.

Although the evolution of the IR spectra of **7c** and **19b** gave useful information about the lithiated intermediates involved in the reaction, and their relative lifetimes, we found that in situ IR monitoring of the rearrangement of benzyl carbamate **2c** was the most informative about the detailed reaction pathway (Figure 4 and Scheme 12). In THF or TBME, compound **2c** showed a C=O absorbance at $\tilde{\nu}$ = 1698 $cm^{-1}$. Treatment with *s*BuLi (1.1 equiv) in THF trans-



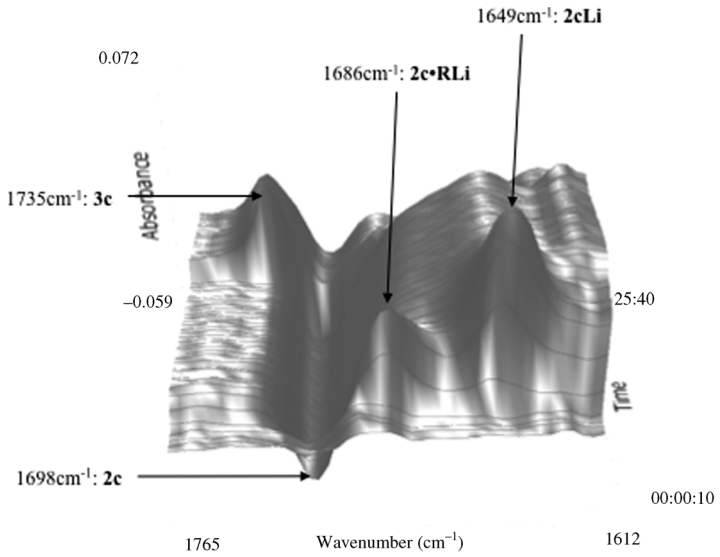
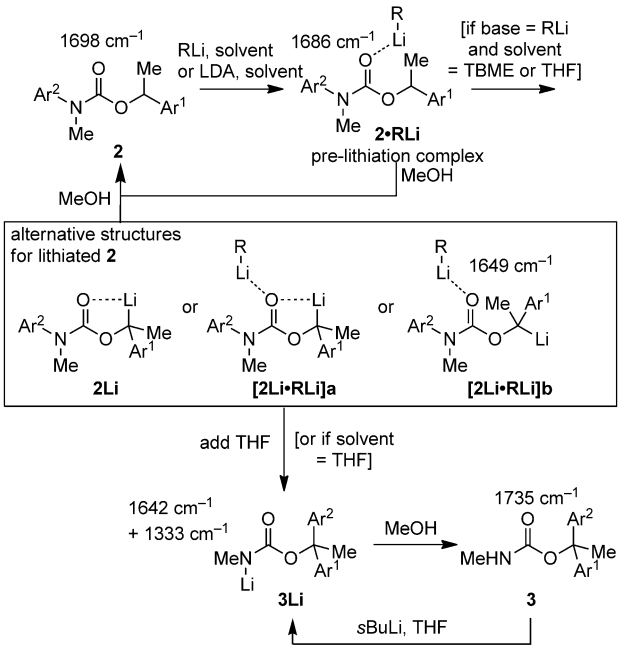




Figure 4. The in situ IR spectra of the rearrangement of **2c** during the reaction using *s*-BuLi at −60 °C. a) A three-dimensional plot of absorbance versus wavenumber versus time and b) a difference spectrum, created by subtracting the initial spectrum of **2c**.

formed this signal directly into one at $\tilde{\nu}$ = 1642 $cm^{-1}$, which we assign to **3cLi**, and addition of MeOH returned the carbamate **3c** with a C=O stretching frequency of $\tilde{\nu}$ = 1735 $cm^{-1}$. A similar peak, at $\tilde{\nu}$ = 1646 $cm^{-1}$ was observed when LDA (1.5 equiv) was used as the base. Evidence that the absorption at $\tilde{\nu}$ = 1642 $cm^{-1}$ arises from the product anion **3cLi** was obtained by treating **3c** with *s*BuLi in THF; the spectrum assigned to **3cLi** reappears under these conditions (see the Supporting Information).

In the absence of THF, the rearrangement was much slower (Figure 4a). Treatment of **2c** in TBME at −60 °C with *s*BuLi (2 equiv) gave a transient absorbance at $\tilde{\nu}$ =




Scheme 12. Intermediates proposed in the rearrangement of **2c**. Solvation of the lithium cation is assumed but not explicitly shown.

1686 $cm^{-1}$, which then gave way over a period of minutes to a band at $\tilde{\nu}=1649\ cm^{-1}$. These bands were assigned by quenching the reaction with MeOH once the band at $\tilde{\nu}=1649\ cm^{-1}$ had appeared. Since this quenching reaction regenerated the starting material **2c** and not product **3c**, we assign the absorbance at $\tilde{\nu}=1649\ cm^{-1}$ to a structure corresponding to **2cLi**, and propose that the transient absorption at $\tilde{\nu}=1686\ cm^{-1}$ is the pre-lithiated complex **2c·RLi**.[36,37] When **2c** was treated with *s*BuLi in toluene at −60 °C, only the absorbance at $\tilde{\nu}=1686\ cm^{-1}$ was observed, indicating that under these conditions, complexation may take place, but not deprotonation. After a reaction time of 30 min, addition of TMEDA (1 equiv) indicated regeneration of the starting material **2c**, probably by decomplexation of the species **2·RLi**. A similar outcome was obtained by using LDA (3.5 equiv) in TBME at −60 °C, which produced a band at $\tilde{\nu}=1690\ cm^{-1}$. After stirring for 1 h, addition of $CD_3OD$ to the reaction mixture resulted in the recovery of the starting material **2c** with no deuterium incorporation (see the Supporting Information). Computational results presented below indicate that the absorption at $\tilde{\nu}=1649\ cm^{-1}$ is best modelled by a complex **[2Li·RLi]b** in which the intramolecular interaction in **2Li** or the alternative structure **[2Li·RLi]a** is absent (Scheme 12). This unexpected result appears to arise from steric interactions between the second equivalent of LDA and the solvated lithium bond to the carbanion centre.

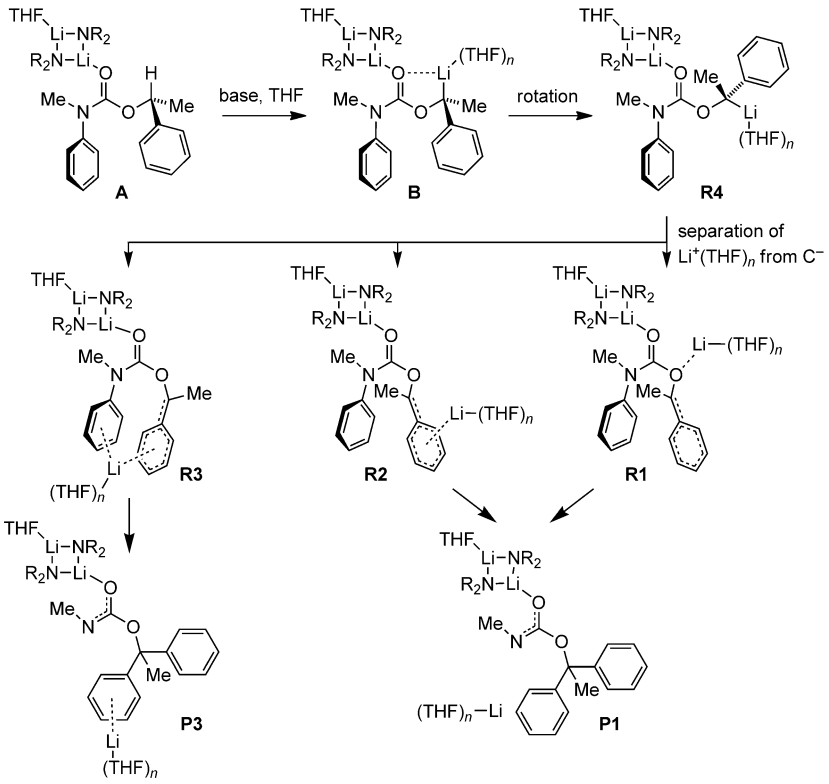
Conversion of the solution of **2cLi** formed from **2c** with *s*BuLi in TBME to **3cLi** was achieved by adding 4 equivalents of THF to the reaction mixture in order to promote the rearrangement. Little change in the IR spectrum was observed, but adding MeOH after 90 min generates a new peak at $\tilde{\nu}=1735\ cm^{-1}$, corresponding to the rearranged carbamate **3c**. The entire course of the reaction is illustrated in Figure 4a, with the intermediates highlighted more clearly in Figure 4b, which shows a difference spectrum, created by subtracting the initial spectrum of **2c**.

It is notable that $\tilde{\nu}_{C=O}$ for lithiated carbamate **2cLi** and the product carbamate anion **3cLi** are very similar. However, the spectrum of **3cLi** also shows a characteristic peak at $\tilde{\nu}=1333\ cm^{-1}$, which is absent from the spectrum of **2cLi**. As shown in the Supporting Information, this peak grew progressively with time, allowing us to monitor the progress of the rearrangement pathway. No other intermediates were observed along the reaction pathway.

**Computational strategy and details**: To shed light on the mechanistic features of the aryl migrations described herein and building on our previous work,[5] appropriate models were constructed involving the benzylic carbamate **2a** in its metallated form **2aLi** and the base LDA, with THF as the solvent. The potential-energy surface for the reaction was obtained by using electronic-structure calculations employing DFT. Properly characterised minima and transition structures (TSs) were located at the B3LYP/6-31G level, giving both vibrational frequencies and starting structures for optimisation at the B3LYP/6-31++G** level. The structures and energetics quoted herein are for the larger basis, with thermodynamic and zero-point corrections from the smaller basis. All calculations were carried out with the Gaussian suite of programmes.[39] In our previous study of the stereospecific intramolecular arylation of lithiated ureas,[38] we found that the major features of the potential-energy surfaces for both retention and inversion of stereochemistry are unchanged when the M06-2X, rather than the B3LYP, functional is employed. For this reason, we have not investigated the effects of different functionals in this case.

We first note that a crystal structure of an LDA–THF complex[40] shows a dimer with each $Li^+$ ion being coordinated to a single THF molecule and sharing two amide ligands with the other $Li^+$ ion. In the model used here, the carbonyl oxygen of the carbamate **2a** replaces one of the THF molecules of this dimer. Thus, our model (Scheme 13) involves one explicit LDA dimer coordinated to the carbonyl oxygen of the carbamate **2a** (**A**), a structure corresponding to the pre-lithiated complex indicated by the in situ IR studies. Furthermore, we assume that deprotonation to form **2aLi** initially gives the reactant structure **B** in which the carbanion is bound to a solvated lithium ion. In view of the experimental observation that excess base facilitates the reaction our model has a dimer of LDA coordinated to the carbonyl oxygen atom. In our corresponding study of lithiated ureas,[38] we found that LDA facilitated the breaking of the intramolecular Li-O(=C) bond in **B**, a change in structure necessary for the substrate to adopt the reactive conformation. As the precise degree of solvation of the lithium ion is unknown, we have considered a model in which the ion is solvated by three THF molecules. As in our previous study of lithiated ureas,[38] we do not consider further implicit sol-




Scheme 13. Structures along the computed reaction pathways.

vation in our model, in line with the findings of Streitwieser et al.,[41] who found that the integral equation polarisable continuum model (IEPCM) was poor at predicting the solvation energies of a range of organic species in THF, and in the absence of bulk solvation, p*K*(Li) values for a range of lithium compounds were well predicted.

Our strategy to understand the mechanism of the 1,4-aryl shift was to search for the transition structures (TSs), and to follow these back to the reactants, and forward to the products. This revealed the corresponding reactant structures and the changes that occur as the TSs are formed from them. Transition structures for the reactions leading to aryl migration were located that gave products in which either retention or inversion of configuration at the carbanion centre had occurred. We found two types of structure leading to inversion of stereochemistry. In one of the two structures, $\{Li(thf)_3\}^+$ was bound to the carbamate oxygen atom (Figure 5a, TS1), whereas in the other it was bound to the phenyl ring adjacent to the carbanion centre (Figure 5b, TS2). A third transition structure (Figure 5c, TS3) in which the solvated lithium species was located between the two phenyl groups was found that led to retention of stereochemistry. We have previously shown[38] that in the case of the corresponding reaction of lithiated ureas, retention of stereochemistry occurs via a transition structure analogous to TS3.

Our strategy of determining the transition structures, and then following these back to the corresponding reactant, led to three different reactant conformations that were higher in energy than the lowest-energy reactant we have located, (R4, Figure 5d). In R4, $Li^+$ is clearly bound to the carbanion centre (at a distance of 2.20 Å). In the three reactant configurations this distance is increased considerably to free up the carbanion lone pair for nucleophilic attack. This charge separation is facilitated by solvation of the lithium cation, and explains why coordinating solvents, such as THF and DMPU, accelerate the reaction. In Figure 5, we show both the reactants and the corresponding transition structures and it is clear how the different reactant conformations give rise to the different transition structures. The reactant structure leading to retention of configuration (R3, Figure 5c) is of considerably higher energy than the lowest energy minimum (R4, Figure 5d; by 82 kJ mol$^{-1}$), whilst those leading to inversion (R2, Figure 5b and R1, Figure 5a) are higher by 36 and 46 kJ mol$^{-1}$, respectively (Table 3). The stability of R4 relative to intramolecularly coordinated structures such as **B**, which are usually assumed for such lithiated carbamates (Scheme 12), results from the reduction in the steric interaction between the LDA coordinated to the carbonyl group and the solvated lithium cation bound to the carbanion, and the associated increase in entropy.

We now discuss the three mechanisms involving these reactant and transition structures. For retention of configura-

Table 3. Relative energies [kJ mol$^{-1}$] of stationary structures.

| Reaction and stereospecificity | Structure | Free energy |
|---|---|---|
| lowest-energy minimum | R4 | 0.0 |
| retention[a] | R3 | 81.5 |
| | TS3 | 81.3 |
| | P3 | −66.0 |
| inversion (with $Li^+$ migrating to O) | R1 | 45.7 |
| | TS1 | 62.4 |
| | P1 | −67.7 |
| inversion (with $Li^+$ migrating to the benzylic ring) | R2 | 36.0 |
| | TS2 | 70.7 |
| | P2 | −48.3 |
| attack on C=O | R5 | 60.7 |
| | TS5 | 75.1 |
| | P5 | −93.1 |

[a] TS3 is of marginally lower free energy than R3 due to zero-point and thermodynamic corrections, but is of higher energy (by 16 kJ mol$^{-1}$) if electronic energy alone is considered.

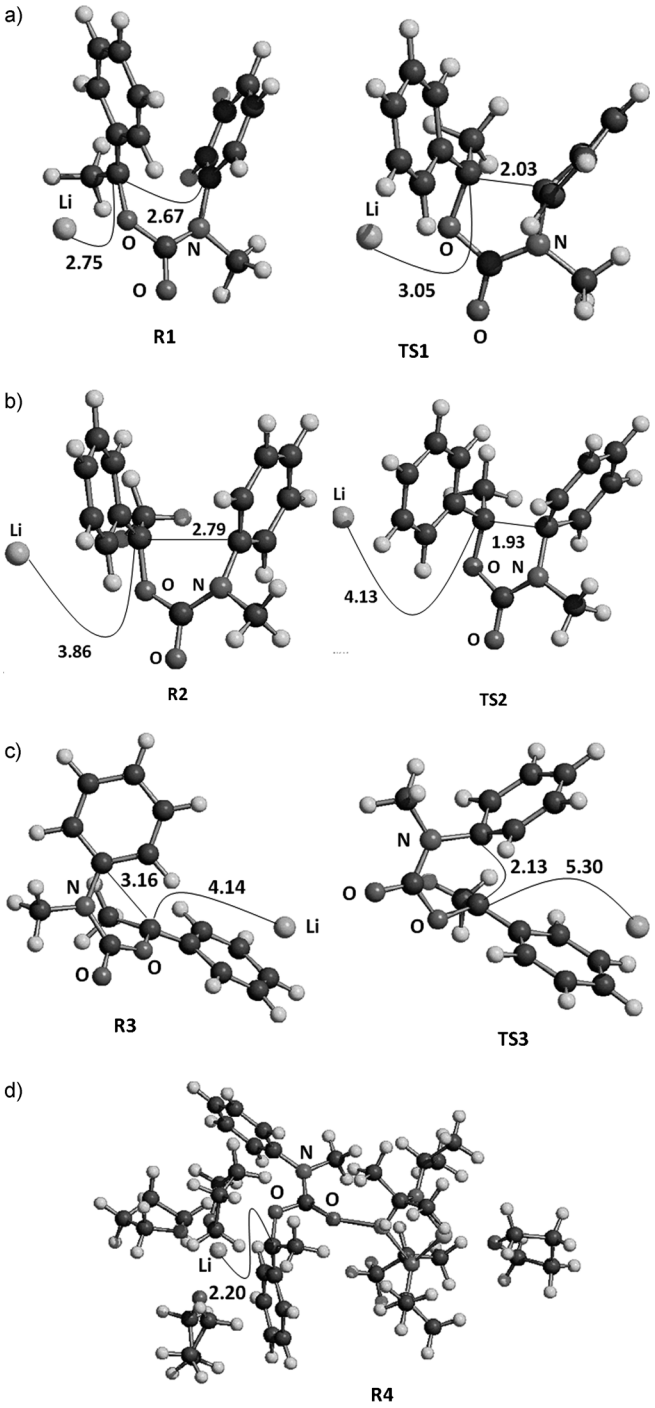



Figure 5. Optimal structures along the reaction pathways. For clarity LDA and THF have been omitted (except in R4). a) Reactant R1 and transition structure TS1 leading to inversion of stereochemistry; b) reactant R2 and transition structure TS2 leading to inversion of stereochemistry; c) reactant R3 and transition structure TS3 leading to retention of stereochemistry; and d) the lowest energy reactant, R4.

tion to take place, via TS3 (Figure 5c), the solvated $Li^+$ ion in the reactant structure (R4) has to migrate from the carbanion to the adjacent ring (R3), thereby freeing the carbanion lone pair for nucleophilic attack on the remote phenyl ring. This migration is facilitated by the conjugation of the carbanion lone pair with the phenyl group, further enhanced by interaction of the phenyl ring with the lithium cation. Such conjugation restricts the free rotation of the phenyl ring and thus provides a "memory" of the configuration at the carbanion centre, despite the lack of a C–Li bond. Thus, although the stereogenic carbanion centre has become planar by the migration of the $Li^+$ ion, the original stereochemical disposition of the groups around it is maintained.

Both transition structures TS3 and TS2, leading to retention and inversion, respectively, involve the interaction of the solvated $Li^+$ species with the benzyl ring. Structure TS2 (Figure 5b) differs from TS3, which was previously discussed, in that the lithium ion lies on the other face of the phenyl group, and thus is unable to stabilise the developing negative charge on the ring suffering nucleophilic attack. In structure TS2, the length of the forming C···C bond is 1.93 Å, which is shorter than in the transition structure that leads to retention of stereochemistry (TS3). The transition structure TS2 leads to inversion of stereochemistry (TS2, Figure 5b) because the forming C–C bond is orientated in the opposite direction to the original C–Li bond. In transition structure TS3, C–C bond formation is in the same direction as the original Li–carbanion bond and leads to retention of configuration.

In the transition structure TS1 and the corresponding reactant (R1, Figure 5a), the $\{Li(thf)_3\}^+$ is bound to and in the plane of the carbamate group, requiring a 1,2-shift of the $Li^+$ cation. This $Li^+$ shift from the carbon atom to the in-plane oxygen lone pair requires conformational changes from the minimum-energy reactant structure so that the $Li^+$ is now in the plane of the carbamate and adjacent to the oxygen lone pair. We note that the other lone pair on oxygen is not available, being conjugated with the carbonyl group. Following the transfer of $Li^+$ to the oxygen atom, the carbanion is neatly arranged for reaction. Indeed, the carbanion is slightly pyramidal, as is the phenyl carbon atom that is attacked, and thus the bond has started to form. This mechanism gives rise to inversion because moving the lithium into the plane of the carbamate, prior to its transfer to the oxygen atom, results in the Li–C bond pointing away from the remote phenyl group.

We now consider the energetics of the three reactions we have identified (Table 3). We find that the transition structures for retention (TS3) and inversion (TS1 and TS2) lie, respectively, 81, 62 and 71 kJ mol$^{-1}$ above the lowest energy reactant structure (R4). However, the corresponding three reactant structures (R1, R2 and R3) are of considerably higher energy than this lowest energy structure (R4) so that the barriers for reaction from these structures are considerably lower, all being below 35 kJ mol$^{-1}$. Thus, our calculations clearly predict that inversion is favoured. TS3, leading to retention, is higher in energy by 19 kJ mol$^{-1}$ than the more favoured route (via TS1) for inversion, which involves a $Li^+$–O interaction. However, we note that the alternative transition structure for inversion, TS2, having a $Li^+$–phenyl in-

Table 4. Harmonic vibrational frequencies [$cm^{-1}$] and intensities [$km\,mol^{-1}$] for stationary structures.

| Species | Mode | Frequency | Intensity |
|---|---|---|---|
| carbamate **2a** | C=O stretch | 1693 | 344 |
| | ring modes | 1643–1666 | 3–105 |
| carbamate with LDA, **2a**·RLi | mixed C=O and ring modes | 1652, 1672 | 363, 373 |
| | ring modes | 1644–1665 | 1-75 |
| R4 | mixed C=O and ring C–H modes | 1638, 1642, 1650 | 259, 263, 167 |
| R1 | mixed C=O stretch and ring modes | 1619, 1624 | 518, 274 |
| | ring modes | 1578–1659 | 23–201 |
| P1 | N=C(-O)-N modes | 1702,1294 | 350, 244 |
| | phenyl ring stretches | 1636–1661 | 1–8 |
| *N*-protonated product **3a** | C=O | 1745 | 383 |
| product anion coordinated to $Li(thf)_3$ through carbamate N **3Li** | N-C(=O)-O | 1335, 1654 | 237, 502 |

teraction, is only $8\,kJ\,mol^{-1}$ higher in energy, so that inversion by both mechanisms is clearly feasible. Although this energy difference is quite small, we can speculate as to the origin of the preferred pathway, bearing in mind that $S_NAr$ reactions usually need anion stabilising groups to facilitate reaction. The key factor would appear to be the lack of stability of the anion centre once the $Li^+$ is bound to the carbamate oxygen atom. This is in line with a comparison of the stationary structures on the alternative pathways, and in the two reactive conformers (R1 and R2), the bond-forming C–C separation for the preferred pathway is shorter in the reactant (R1) and longer in the transition structure (TS1). Thus, in the more stable reactant structure (R2), the charge on the conjugated carbanion is stabilised by the $Li^+$ over the phenyl ring, whilst the lower-energy transition structure (TS1), which lacks this stabilisation and is earlier than the alternative structure, readily undergoes nucleophilic attack to yield a stable anion through aryl transfer.

In a corresponding study of the rearrangement of a lithiated urea, a dearomatised naphthyl intermediate was characterised by NMR spectroscopy, and was predicted to be stable by DFT calculations.[38] In the case of the carbamates studied herein, no such intermediates were detected experimentally, and they could not be located on our computed reaction pathways. We therefore propose that this $S_NAr$ reaction proceeds, unusually, without a dearomatised intermediate.

We have also studied the corresponding 1,2-aryl transfer of the benzyl carbamate, which proceeds via a cyclic three-membered transition structure, and may occur with *N*-alkyl, rather than *N*-aryl, carbamates.[22] We find that this TS is $75\,kJ\,mol^{-1}$ above our lowest reactant minimum and is thus $13\,kJ\,mol^{-1}$ above our calculated barrier for the observed 1,4-aryl shift reaction. Thus, it would appear that the energetic penalty of forming this strained cyclic transition structure is decisive in favouring the observed attack on the $\pi$ system of the phenyl group.

We now discuss the harmonic vibrational frequencies for the various minimum-energy species that our computations have identified along the reaction pathway of the benzyl carbamate (Table 4). Our aim is to use these values to aid in the identification of the species found in the IR spectra we have previously described. We note that the experimental data are for compound **2c**, having a chlorine substituent on one phenyl ring, which is absent in our model employing **2a**.

We focus on the changes in the C=O stretching frequency that we have observed experimentally during the rearrangement of **2c**. In the neutral reactant, the C=O stretch is computed to occur at $\tilde{\nu}=1693\,cm^{-1}$, close to the experimentally determined band at $\tilde{\nu}=1698\,cm^{-1}$. This good agreement gives us confidence that we can understand the variation in the C=O frequency along the reaction pathway. The addition of LDA leads to a peak at $\tilde{\nu}=1686\,cm^{-1}$, which correlates with the computed peak at $\tilde{\nu}=1672\,cm^{-1}$ for structure A (Scheme 13), corresponding to a pre-lithiated complex having the LDA dimer coordinated to the carbonyl oxygen atom. We predict a second nearby peak at $\tilde{\nu}=1652\,cm^{-1}$, in which the C=O stretching band is mixed with the ring C–H modes. We have previously discussed that our calculations have identified a low-energy lithiated carbamate structure (R4), which, following conformational changes, gives the structures that actually undergo reaction. This structure (R4) is predicted to have strong peaks at $\tilde{\nu}=1638$, 1642 and $1650\,cm^{-1}$, which are mixtures of C=O and C–H ring modes. Experimentally, a peak at $\tilde{\nu}=1649\,cm^{-1}$ is seen to grow following the addition of LDA to the benzyl carbamate **2c**, which we thus assume corresponds to our computed structure R4. We have found other structures, similar to R4, including those with intramolecular Li–O coordination as in **B**, and computed their harmonic frequencies, as well as those for the higher-energy structures (R1, R2, R3) that lead to reaction. However, we find that none of these structures give the excellent prediction of the observed IR spectrum of lithiated **2c** that is provided by structure R4.

For the product anion in which the solvated $Li^+$ is coordinated to the nitrogen atom of the carbamate, we predict intense bands at $\tilde{\nu}=1335$ and $1654\,cm^{-1}$, values which are in excellent agreement with the peaks observed experimentally at $\tilde{\nu}=1333$ and $1642\,cm^{-1}$ for **3cLi**. In an alternative structure (P1, the product from TS1, Scheme 13 and Figure 5), in which the solvated cation remains bound to the carbamate oxygen after aryl transfer, the corresponding computed frequencies are $\tilde{\nu}=1294$ and $1702\,cm^{-1}$, indicating that, in the final species generated on completion of the rearrangement, lithium has migrated to the nitrogen atom of the carbamate anion. After protonation of the anion, the computed carbon-

yl stretching frequency is $\tilde{\nu}=1745\ cm^{-1}$, which is close to the experimentally determined value of $\tilde{\nu}=1735\ cm^{-1}$

## Conclusion

The rearrangement of lithiated carbamates carrying *N*-aryl substituents, already reported for *O*-benzyl carbamates, is a characteristic reactivity also of *O*-allyl, *O*-vinyl and *O*-propargyl carbamates. The products of the rearrangements contain quaternary oxygen-substituted centres, and the product carbamates may be converted into tertiary alcohols. Racemisation of the organolithium compounds means that products with high enantiomeric ratios are difficult to obtain, but in cases in which enantiomeric enrichment is preserved, inversion of configuration during the rearrangement is observed. A combination of in situ IR measurements and electronic-structure calculations has allowed us to identify a number of intermediates in the stereospecific intramolecular arylation of lithiated *O*-benzyl carbamates. Coordination of the starting carbamate with the base generates a pre-lithiated complex, detectable by IR spectroscopy in the absence of THF that has the LDA dimer coordinated to the carbonyl oxygen atom. Deprotonation in coordinating solvents gives a lithiated carbamate, for which we propose a non-intramolecularly coordinated structure on the basis of its modelled IR spectrum. The computations predict that movement of the solvated $Li^+$ is required to give new reactant structures that differ in the location of the $Li^+$ ion and can lead to different stereochemical outcomes. The most energetically favoured pathway is 1,2-migration of $Li^+$ from the carbanion centre to the adjacent carbamate oxygen atom, followed by an aryl shift from N to C with inversion of configuration at the carbanion centre. An alternative reactant structure, generated by migration of the $Li^+$ bound to the face of the adjacent phenyl ring, also results in inversion of configuration but with a slightly higher barrier. A reactant structure in which the solvated $Li^+$ ion is found between the two phenyl rings gives rise to retention of configuration but with a rather higher barrier. A comparison of the IR data with frequency calculations gives good agreement and in two ambiguous cases allows structures to be assigned to intermediates. Thus, the lithiated starting material (in the presence of excess base) apparently lacks the intramolecular Li–O interaction generally proposed in lithiated carbamates, and the product carbamate anion is an *N*-lithio, rather than an *O*-lithio, species.

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[1] a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; c) B. Goldfuss, *Synthesis* **2005**, 2271; d) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454; e) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873; f) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853; g) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; h) D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 268; i) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407.

[2] J. Clayden, M. Donnard, J. Lefranc, D. J. Tetlow, *Chem. Commun.* **2011**, *47*, 4624.

[3] J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582.

[4] a) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778; b) H. K. Scott, V. K. Aggarwal, *Chem. Eur. J.* **2011**, *17*, 13124; c) M. Shimizu, *Angew. Chem.* **2011**, *123*, 6122; *Angew. Chem. Int. Ed.* **2011**, *50*, 5998.

[5] J. Clayden, W. Farnaby, D. M. Grainger, U. Hennecke, M. Mancinelli, D. J. Tetlow, I. H. Hillier, M. A. Vincent, *J. Am. Chem. Soc.* **2009**, *131*, 3410.

[6] A. M. Fournier, R. A. Brown, W. Farnaby, H. Miyatake-Ondozabal, J. Clayden, *Org. Lett.* **2010**, *12*, 2222.

[7] J. Clayden, J. Dufour, D. Grainger, M. Helliwell, *J. Am. Chem. Soc.* **2007**, *129*, 7488.

[8] J. Clayden, U. Hennecke, *Org. Lett.* **2008**, *10*, 3567.

[9] R. Bach, J. Clayden, U. Hennecke, *Synlett* **2009**, 421.

[10] P. MacLellan, J. Clayden, *Chem. Commun.* **2011**, *47*, 3395.

[11] A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097.

[12] *Topics in Organometallic Chemistry, Vol. 5, Organolithiums in Enantioselective Synthesis* (Ed.: D. M. Hodgson), Springer, Berlin, **2003**.

[13] a) D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, *Angew. Chem.* **1981**, *93*, 1106; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1024; b) D. Hoppe, T. Krämer, J.-R. Schwark, O. Zschage, *Pure Appl. Chem.* **1990**, *62*, 1999; c) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282.

[14] a) D. Hoppe, T. Krämer, *Angew. Chem.* **1986**, *98*, 171; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 160; b) T. Krämer, D. Hoppe, *Tetrahedron Lett.* **1987**, *28*, 5149.

[15] a) O. Zschage, J.-R. Schwark, D. Hoppe, *Angew. Chem.* **1990**, *102*, 336; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 296; b) O. Zschage, J.-R. Schwark, T. Krämer, D. Hoppe, *Tetrahedron* **1992**, *48*, 8377.

[16] a) D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69; b) O. Zschage, D. Hoppe, *Tetrahedron* **1992**, *48*, 5657; c) H. Paulsen, C. Graeve, D. Hoppe, *Synthesis* **1996**, 141.

[17] a) K. Behrens, R. Fröhlich, O. Meyer, D. Hoppe, *Eur. J. Org. Chem.* **1998**, 2397; b) T. Hémery, R. Huenerbein, R. Frohlich, S. Grimme, D. Hoppe, *J. Org. Chem.* **2010**, *75*, 5716.

[18] a) M. Seppi, R. Kalkofen, J. Reupohl, R. Fröhlich, D. Hoppe, *Angew. Chem.* **2004**, *116*, 1447; *Angew. Chem. Int. Ed.* **2004**, *43*, 1423; b) J. Reuber, R. Fröhlich, D. Hoppe, *Org. Lett.* **2004**, *6*, 783–786; c) E.-U. Würthwein, D. Hoppe, *J. Org. Chem.* **2008**, *73*, 9055.

[19] S. Dreller, M. Dyrbusch, D. Hoppe, *Synlett* **1991**, 397.

[20] C. Schultz-Fademrecht, B. Wibbeling, R. Fröhlich, D. Hoppe, *Org. Lett.* **2001**, *3*, 1221.

[21] Carbamates were made by treating allylic alcohols with aryl isocyanates and methylating the products under standard conditions. See the Supporting Information for further details.

[22] a) P. Zhang, R. E. Gawley, *J. Org. Chem.* **1993**, *58*, 3223; b) S. Superchi, N. Sotomayor, G. Miao, J. Babu, M. G. Campbell, V. Snieckus, *Tetrahedron Lett.* **1996**, *37*, 6061; c) G. B. C. A. Slana, M. S. de Azevedo, R. S. C. Lopes, C. C. Lopes, J. N. Cardoso, *Beilstein J. Org. Chem.* **2006**, *2*, 1.

[23] D. J. Tetlow, U. Hennecke, J. Raftery, M. J. Waring, D. S. Clarke, J. Clayden, *Org. Lett.* **2010**, *12*, 5442.

[24] a) X. Wei, R. J. K. Taylor, *Chem. Commun.* **1996**, 187; b) X. Wei, P. Johnson, R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1109; c) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1997**, *38*, 6467; d) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1996**, *37*, 4209; e) H. Felkin, G. Swierczewski, A. Tambuté, *Tetrahedron Lett.* **1969**, *10*, 707; f) T. Kato, S. Marumoto, T. Sato, I. Kuwajima, *Synlett* **1990**, 671; g) S.

  

Marumoto, I. Kuwajima, *Chem. Lett.* **1992**, 1421; h) S. Marumoto, I. Kuwajima, *J. Am. Chem. Soc.* **1993**, *115*, 9021.
[25] A. M. Fournier, J. Clayden, *Org. Lett.* **2012**, *14*, 142.
[26] H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355.
[27] R. Ramesh, Y. Chandrasekaran, R. Megha, S. Chandrasekaran, *Tetrahedron* **2007**, *63*, 9153.
[28] J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, **2002**.
[29] V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237.
[30] T. I. Yousaf, R. L. Williams, I. Coldham, R. E. Gawley, *Chem. Commun.* **2008**, 97.
[31] Racemic products were also formed in the presence of O'Brien's (+)-sparteine surrogate [P. O'Brien, *Chem. Commun.* **2008**, 655], or when racemic starting materials were deprotonated in the presence of an alkyllithium/sparteine complex, reactions carried out in an attempt to induce kinetic resolution of the chiral starting material or dynamic kinetic or thermodynamic resolution of the intermediate organolithium [A. Basu, S. Thayumanavan, *Angew. Chem.* **2002**, *114*, 740; *Angew. Chem. Int. Ed.* **2002**, *41*, 716]. A recent publication [M. Sasaki, H. Ikemoto, M. Kawahata, K. Yamagushi, K. Takeda, *Chem. Eur. J.* **2009**, *15*, 4663] suggested that electron-donating groups also reduce racemisation rates in benzyl- and allylithium compounds, but rearrangement of the *para*-methoxy analogue of **7d** gave no improvement in the results.
[32] J. Clayden, M. Donnard, J. Lefranc, A. Minassi, D. J. Tetlow, *J. Am. Chem. Soc.* **2010**, *132*, 6624.
[33] K. Matsumura, S. Hashigushi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738.
[34] The absolute configuration of the product of the 1,2-acyl shift is unknown, but such 1,2-acyl shifts are reported to proceed with retention of configuration: K. Tomooka, H. Shimizu, T. Inoue, H. Shibata, T. Nakai, *Chem. Lett.* **1999**, 759.
[35] X.-B. Jiang, M. van den Berg, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2004**, *15*, 2223.
[36] D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260; see also: N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien, I. Coldham, *J. Am. Chem. Soc.* **2012**, *134*, 5300.
[37] D. J. Pippel, G. A. Weisenburger, N. C. Faibish, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 4919.
[38] a) D. M. Grainger, A. Campbell Smith, M. A. Vincent, I. H. Hillier, A. E. H. Wheatley, J. Clayden, *Eur. J. Org. Chem.* **2012**, 731; b) J. Lefranc, A. M. Fournier, G. Mingat, S. Herbert, T. Marcelli, J. Clayden, *J. Am. Chem. Soc.* **2012**, *134*, 7286.
[39] Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.
[40] P. G. Williard, J. M. Salvino, *J. Org. Chem.* **1993**, *58*, 1.
[41] A. Streitwieser, J. R. Reyes, T. Singhapricha, S. Vu, R. Shah, *J. Org. Chem.* **2010**, *75*, 3821.

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