1,2-Carbamoyl Migration on Enantio-enriched α-Lithioalkyl Carbamates Generated with *s*-Butyllithium/Sparteine: Steric Course and Mechanism

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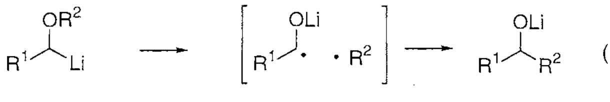
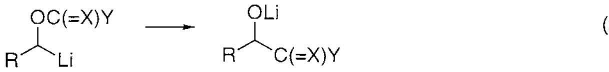
Alkyl *N*,*N*-diisopropylcarbamates, when lithiated with *s*-BuLi/(-)-sparteine in ether at -78 °C followed by warming to room temperature, are shown to undergo the 1,2-carbamoyl migration to give the α-hydroxy amides in >95% ee with complete retention of configuration at the Li-bearing carbanion terminus. An addition-elimination mechanism is proposed.

Some α-lithiated ethers are known to undergo the 1,2-alkyl migration, called [1,2]-Wittig rearrangement, which is now recognized to proceed via the radical cleavage-recombination mechanism (eq 1).[1] Also known is a formally similar type of rearrangement (eq 2) which involves the 1,2-shift of an sp^2-carbon such as CH=CHR[2] and C(=NOMe)Ph[3] on the benzylic lithiums (R=Ph), although it remains unsolved whether they proceed via the radical mechanism or not. Recently we have found, by accident, that an alkyl *N*,*N*-diisopropylcarbamate (**1**), when lithiated with *s*-BuLi/(-)-sparteine,[4] underwent a novel 1,2-carbamoyl shift to produce an enantio-enriched α-hydroxy amide **3** (eq 3).[5] Herein described is the scope and limitation, the steric course at the Li-bearing terminus, and the mechanism of the novel 1,2-carbamoyl migration reaction.



(1)



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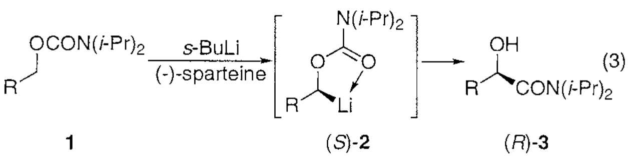
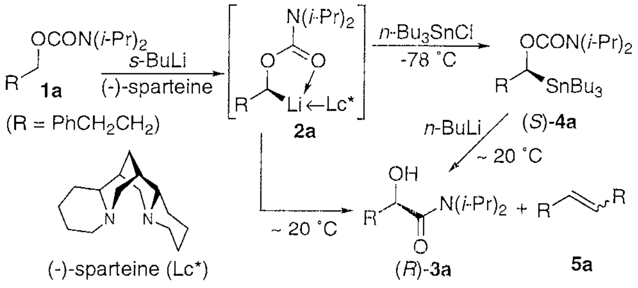


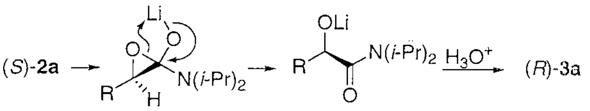
(3)

At first, we examined the asymmetric lithiation/stannylation sequence of carbamate **1a** in order to confirm the absolute configuration of the α-lithio species **2a** involved (Scheme 1). Thus, **1a** was treated with a pre-mixed *s*-BuLi/(-)-sparteine (1.2 equiv. each) in ether at -78 °C and then treated with Bu$_3$SnCl at that temperature to give (*S*)-stannane **4a** in 97% ee.[6] Since the stannylation is known to proceed with complete retention of configuration,[4] the formation of (*S*)-**4a** indicates that the lithio species **2a** is (*S*)-configurated. When (*S*)-**2a** generated in the same way at -78 °C was gradually warmed to room temperature, on the other hand, we found that the (*R*)-α-hydroxy amide **3a**[7] was obtained in 46% yield and 96% ee,[8] along with the olefin **5a** (29 %) as an *E*/*Z* mixture (*E*/*Z* = 86/14).[9] Alternatively, transmetallation[10] of stannane (*S*)-**4a** (>95% ee) with *n*-BuLi in THF at -78 °C in the absence of sparteine followed by warming to 25 °C was found to afford (*R*)-**3a** in 44% yield and >95% ee.[8,11]



Scheme 1.

This stereochemical correlation between (*S*)-**2a** and (*R*)-**3a** reveals that the 1,2-carbamoyl migration occurs with complete retention of configuration at the Li-bearing terminus. That means that the steric course of the present 1,2-shift is opposite in sense to that of the [1,2]-Wittig rearrangement which has been proved to proceed predominantly with inversion of configuration,[1d,12] thereby allowing us to exclude the radical cleavage-recombination mechanism for the 1,2-carbamoyl migration. Instead, we now propose the addition-elimination pathway in which the intramolecular addition of the Li-bearing carbon to the carbamoyl-carbonyl occurs in completely retentive fashion. (eq 4).



(4)

Next, several attempts to improve the yield were made using **1a** as substrate. Although all the attempts failed, the following observations deserve comment. When Lewis acid such as (*i*-PrO)$_4$Ti, BF$_3$•OEt$_2$, or Me$_3$Al was added to the **2a**-containing solution, the carbamoyl migration was completely suppressed, while addition of LiCl led to a slightly lower yield. Interestingly, addition of 12-crown-4 also suppressed the migration concerned and the use of THF as a co-solvent was not helpful in improving the yield. Finally, we carried out the similar reactions of different carbamates to define the scope of the present carbamoyl migration. Some examples are shown below. Of special interest is that alkyl carbamate **1b** gave the carbamoyl-migrated product in comparable yield and % ee,[13] while a higher yield, albeit lowered % ee, was observed with benzyl carbamate **1c**[14, 15] and much lower yields and % ee were obtained with allylic carbamtes **1d** and **1e**.[16, 17]

In summary, we have shown that enantio-enriched α-lithioalkylcarbamate generated with *s*-BuLi/(-)-sparteine, undergo a novel 1,2-carbamoyl migration in completely retentive fashion at the Li-bearing terminus. Thus, the addition-elimination

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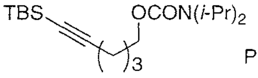
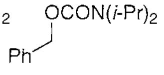
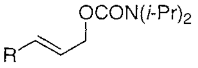


(TBS = *t*-BuMe$_2$Si)

1b, 49%; 97% ee



1c, 67%; 14% ee



1d (R=Ph), 12%; 16% ee
1e (R=Me),19%; 2% ee

pathway has been proposed for the carbamoyl migration. Further works are underway to improve the present migration reaction and prove the mechanism of the vinyl migration reaction depicted in eq 2.

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References and Notes

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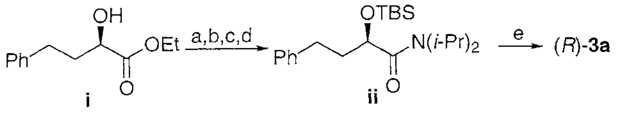
5 A similar 1,2-carbamoyl migration has been observed in α-lithiated benzylic and allylic carbamates. However, any stereochemical and mechanistic discussion have not been made. : a) D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, **23**, 932 (1984). b) P. Zhang and R. E. Gawley, *J. Org. Chem.*, **58**, 3223 (1993). c) S. Superchi, N. Sotomayor, G. Miao, B. Joseph, M. G. Campbell, and V. Snieckus, *Tetrahedron Lett.*, **37**, 6061 (1996). Also noteworthy is that a 1,3-carbamoy migration has been reported on *ortho*-lithiated arylcarbamates: d) M. P. Sibi and V. Snieckus, *J. Org. Chem.*, **48**, 1935 (1983).

6 (*R*)-**4a**; colorless oil; $[\alpha]^{20}_{D}$ +21.9°(*c* 1.00, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33-7.15 (m, 5H), 4.70 (dd, *J* = 4.8, 9.5 Hz, 1H), 4.25-3.60 (m, 2H), 2.77 (ddd, *J* = 5.1, 10.9, 13.6 Hz, 1H), 2.64 (ddd, *J* = 6.3, 10.4, 13.6 Hz, 1H), 2.23 (ddd, *J* = 5.1, 9.5, 14.2 Hz, 1H), 2.05 (dddd, *J* = 4.8, 6.3, 10.9, 14.2 Hz), 1.53-1.43 (m, 6H), 1.40-1.20 (m, 6H), 1.22 (d, *J* = 7.1 Hz, 12H), 0.92-0.85 (m, 15H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.4, 142.3, 128.5, 125.86, 70.94, 47.0-44.0 (m), 36.7, 34.5, 29.1, 27.5, 22.0-20.0 (m), 13.6, 9.7. The % ee was determined by the HPLC analysis using a Daicel CHIRALCEL OD [hexane:*i*-PrOH = 600:1 v/v; t_R = 11.8 min (*S*) and 14.4 min (*R*)]. The *S* configuration was assigned by conversion to the known (*R*)-hydroxy stannane via Dibal-H reduction: K. Tomooka, T. Igarashi, and T. Nakai, *Tetrahedron Lett.*, **35**, 1913 (1994).

7 (*R*)-**3a**; white solid; mp 39 °C; $[\alpha]^{25}_{D}$ +8.6°(*c* 0.38, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35-7.15 (m, 5H), 4.23 (td, *J* = 7.2, 2.8 Hz, 1H), 4.13 (d, *J* = 7.2 Hz, 1H), 3.56 (qq, *J* = 6.8 Hz, 1H), 3.41 (qq, *J* = 6.8 Hz, 1H), 2.79 (t, *J* = 7.7 Hz, 1H), 1.85 (dtd, *J* = 14.1, 7.7, 7.2 Hz, 1H), 1.76 (dtd, *J* = 14.1, 7.7, 2.8Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.6, 141.4, 128.4, 128.3, 125.9, 67.3, 47.6, 46.3, 37.5, 32.3, 20.8, 20.6, 20.3, 20.3; Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32 %. Found: C, 72.60; H, 9.21; N, 5.07 %.

8 The enantio-purity of **3a** was determined by ^{1}H NMR assay of the MTPA ester, and the *R* configuration was assigned by comparison of the optical rotation with that of an authentic (*R*)-sample independently prepared from (R)-**i** as depicted below: sample (*R*)-**3a**; $[\alpha]^{25}_{D}$ +8.9° (*c* 0.38, CHCl$_3$).



a, TBSOTf, 2,6-Lutidine; b LiOH, dioxane-H$_2$O; c, SOCl$_2$, CH$_2$Cl$_2$; d, HN(*i*-Pr)$_2$; e, TBAF, THF

9 Byproduct **5a** is likely to arise from dimerization of the lithium carbenoid species involved.

10 The Sn/Li transmetallation is known to proceed with complete retention of configuration: J. S. Sawyer, A. Kucerovy, T. L. Macdonald, and G. L. MeGarvey, *J. Am. Chem. Soc.*, **110**, 842 (1988), and references cited therein.

11 The high % ee observed in THF is rather surprising in view of Gawley's observation (ref. 5) that a similar reaction of benzyl *N,N*-diethylcarbamate with *s*-BuLi/sparteine resulted in the formation of the carbamoyl-migrated product in racemic form.

12 K. Tomooka, T. Igarashi, and T. Nakai, *Tetrahedron*, **50**, 5927 (1994).

13 (*R*)-**3b**; white solid; mp 105 °C; $[\alpha]^{25}_{D}$ +73.6°(*c* 0.69, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.55 (d, *J* = 5.4 Hz, 1H), 3.94 (qq, *J* = 6.3 Hz, 1H), 3.49-3.37 (m, 2H), 2.63 (m, 1H), 2.21 (ddd, *J* = 7.5, 9.3, 17.5 Hz, 1H), 2.04-1.57 (m, 4H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.9, 161.6, 133.8, 73.7, 50.4, 45.5, 33.6, 32.8, 27.2, 26.1, 24.0, 20.7, 20.5, 20.4, 19.2, -4.0, -4.9; Anal. Calcd for $C_{22}H_{39}NO_2Si$: C, 69.97; H, 10.42; N, 3.71 %. Found: C, 70.48; H, 10.46; N, 3.85 %.

14 **3c**; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.19 (m, 5H), 5.11 (s, 1H), 3.80 (qq, *J* = 6.6 Hz, 1H), 3.35 (qq, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.46 (d, *J* = 6.6 Hz, 3H); HPLC analysis (CHIRALPAK AD, hexane/*i*-PrOH=20/1, t_R=9.9 min (minor) and 12.6 min (major).

15 The extremely low % ee observed here and by Gawley (ref. 5b) is explainable as result of the configurational instability of the benzylic lithium species involved. In fact, a similar sparteine-mediated lithiation of **1c** followed by trapping with Bu$_3$SnCl was formed to stannane **4c** in only 22% ee.

16 The ^{1}H NMR peaks due to the methine proton are δ 4.83 (d, *J* = 6.6, 7.8 Hz), for **3d** and 4.50 (dd, *J* = 6.6, 7.5 Hz) for **3e**.

17 The low yield was and % ee might be explained in terms of the generation of the α- and γ-lihiated species as proved by Hoppe *et al.* (ref. 3b)