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Communication

On the steric course of transmetallations on enantiomerically defined α-carbamoyloxy organolithiums

Katsuhiko Tomooka, Hideo Shimizu, Takeshi Nakai *

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan

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Abstract

The steric courses of the transmetallations of the title organolithiums to the Sn(IV)-, Mg(II)-, Ce(III)-, Zn(II)-, and Cu(I)-species are described. © 2001 Published by Elsevier Science B.V.

Keywords: Transmetallation; Stereochemistry; Phenomena; Organocerium; Organozinc

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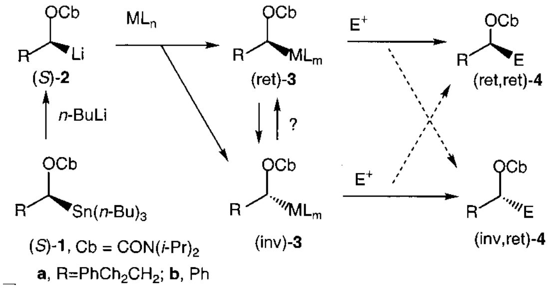
Transmetallation constitutes one of the key processes in organometallic reactions and finds broad synthetic application. However, the exact steric course (retention vs. inversion) of transmetallation processes remains largely undefined and are often hard to elucidate, mainly because in most cases the configurational stabilities of the organometallic species involved are poorly defined or unknown and/or the steric course of the subsequent demetallation process remains obscure. If the organometallic species to be transmetallated is enantiomerically defined and configurationally stable, it would become feasible to elucidate the steric course of transmetallation proceeding at the metal-bearing sp^3-carbon with a high degree of reliability. Disclosed herein is our preliminary report on the stereochemistry of several transmetallations on the enantiomerically defined and configurationally stable α-carbamoyloxy organolithiums [1].



Scheme 1.

Scheme 1 shows our general approach to elucidate the steric course of transmetallation on chiral organolithium **2**, generated in situ from the highly enantio-enriched stannanes (*S*)-**1** which are obtainable via the (−)-sparteine-mediated enantioselective lithiation followed by stannylation [1,2]. Since the Sn/Li transmetallation in general is well established to proceed with complete retention of configuration [3], the steric course of the transmetallation in question could be elucidated from the stereochemistry of the final product **4**, as long as the steric course of the S$_E$2-type reaction of the transmetallated species **3** is reasonably defined. However, note that this approach is only applicable to the cases where product **4** is obtained in reasonably high %ee; otherwise, the steric course remains obscure due to the racemization problem with species **3**.

First, we examined the Li/Sn transmetallation on the chiral α-*N*,*N*-diisopropylcarbamoyloxy organolithiums **2**. Thus, alkylstannane (*S*)-**1a** (> 95%ee) [2] was treated with *n*-BuLi in THF at −78°C to generate (*S*)-**2a**, then trapped with tributyltin chloride to give stannane (*S*)-**1a** [ret-**3a** (M = Sn)] with exactly the same %ee as that of the starting stannane (chiral HPLC, Chiralcel OD). Since the initial Sn/Li transmetallation is retentive [3],

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* Corresponding author. Tel.: + 81-3-57342150; fax: + 81-3-57342885.

E-mail address: takeshi@o.cc.titech.ac.jp (T. Nakai).

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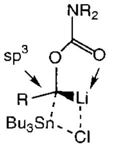
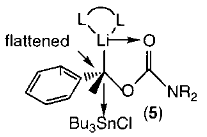
this outcome proves that the Li/Sn transmetallation concerned also proceeds with complete retention of configuration, presumably via the pre-coordination pathway **A**. The same observation had been made by Hoppe's group in the stannylation of the lithio species generated from alkyl carbamates (with a different carbamoyl group) with *s*-BuLi/(−)-sparteine [1,4]. In contrast, a similar Li/Sn transmetallation of benzyllithium **2b**, generated from stannane (*S*)-**1b** (22%ee) [2], was found to result in complete racemization. This observation is not surprising in view of Hoppe's observation that the (−)-sparteine-bound benzyllithium species **2b** is configurationally labile [1]. Thus, this outcome is best explained as a result of the racemization of Li-species **2b** prior to stannylation, and hence the exact steric course of the Li/Sn transmetallation remains obscure. In fact, trapping of **2b** with benzaldehyde that might direct the reaction to the highly retentive course by virtue of its ability to pre-coordinate with lithium also led to complete racemization. Of interest in this context is that the racemic species **2b** once generated from (±)-**1b** was treated with (−)-sparteine followed by stannylation to give stannane **1b** in enantio-enriched form (*S*, 22%). Since the %ee-value is the same as observed in the direct stannylation of the Li-species generated from the benzyl carbamate with *s*-BuLi/(−)-sparteine, the asymmetric induction is likely to occur at the stannylation step, probably under a dynamic kinetic resolution. Here, it should be noted that the complete *inversion* has been observed by Hoppe's group for the stannylation of the α-carbamoyloxy-α-methybenzyllithium **5** (configurationally stable!); they have proposed the pathway **B** [5]. Anyway, these results caution us that the transmetallation stereochemistry of benzylic lithiums is in general more complicated due to the configurational instabilities thereof.

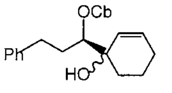


A

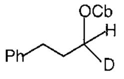


B

Next, our interest was turned to the Li/Mg and Li/Ce transmetallation on alkyllithium (*S*)-**2a**. Thus, (*S*)-**2a**, generated from (*S*)-**1a** (>95%ee), was treated with $MgBr_2$ [freshly prepared from 1,2-dibromoethane and magnesium metal] in THF at −78°C for 1 h and then reacted with 2-cyclohexenone at −5°C or ca. +20°C for 1 h followed by treatment with D_2O to give a diastereomeric mixture of 1,2-adduct (*R*)-**6a** in > 95%ee (HPLC, Chiralcel AD), together with or without the deuterated product **7a**; the yield [diastereomeric ratio (^{1}H NMR assay)] of **6a** was 19% [80:20] at −5°C and 44% [79:21] at +20°C, and the yield of **7a** was 50% at −5°C and 0% at +20°C. The (*R*)-configuration of the chiral center in question of adduct **6a** was assigned after hydrogenation (H_2, Pd-C) forming the cyclohexyl derivative which was identical in chiral HPLC with the authentic (*R*)-isomer obtained via reaction of Li-species (*S*)-**2a** with cyclohexanone. It thus appears likely that the Mg-species thus generated is configurationally and chemically more stable (up to +20°C) than Li-species **2a** which is known to undergo the 1,2-carbamoyl migration at −20°C [2]. Of special note in this context is Hoffmann's recent observation that a chiral, *sec*-alkylmagnesium chloride is configurationally stable in THF up to −30°C [6]. A similar transmetallation with $CeCl_3$ at −78°C afforded 50% yield of (*R*)-**6a** in 94%ee with dr = 91:9; none of **7a** was obtained. Interestingly, the reaction of the Mg- and Ce-species provided a significantly higher diastereoselectivity than that of Li-species **2a** (dr = 63:37, 68% yield at −78°C). McGarvey et al. have reported that the Li/Mg transmetallation of an α-(benzyloxymethoxy)alkyllithium leads to an enhanced diastereoselectivity in the reaction with benzaldehyde [7]. Most significantly, in both cases, the absolute configuration at the chiral center in question of the final product and its enantio-purity are essentially the same as those of Li-species **2a**, suggesting strongly that both the Li/Mg and Li/Ce transmetallation proceed with almost complete retention of configuration through the pre-coordination pathway like **A**; the inversion/inversion pathway is very unlikely since carbonyl compounds usually react with organometallics in retentive fashion through the pre-coordination with the metal center.

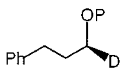


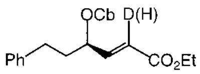
(*R*)-**6a**

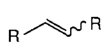


7a

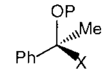
Furthermore, we examined the Li/Zn and Li/Cu transmtallation on alkyllithium **2a**. Thus, (*S*)-**2a**, generated from (*S*)-**1a** (>95%ee), was treated with $ZnBr_2$ in THF (−78°C, 1 h) and then reacted with ethyl propiolate (1 h) followed by the addition of D_2O. While none of the propiolate adduct was obtained (indicating the formation of a Zn-species), the deuterated product (*S*)-**7a** was obtained in 73% yield and >95%ee. Note that under the same conditions Li-species **2a** reacted completely with the propiolate to give a complex mixture. The (*S*)-configuration and enantio-purity of **7a** were determined by ^{1}H NMR comparisons of the (*R*)-MTPA ester **7a′** [prepared via reduction (deprotection) with DIBAL-H [8] followed by reaction with (*R*)-MTPACl] with the authentic samples derived in the same way from (±)- and (*S*)-**7a** (>95%ee) obtained via direct deuteration of the Li-species (±)- and (*S*)-**2a**, respectively. Given the reasonable postulate that the deuteration concerned occurs in retentive fashion [9], this outcome reveals that the Li/Zn transmetallation proceeds in a completely retentive manner. Of special note in this context is Normant and Marek's observation [9] that the Li/Zn transmetallations of the benzylic lithiums generated via addition of *n*-BuLi onto (*E*)-cinnamyl alcohol and the *N*,*N*-dimethylamino derivative occur at completely *invertive* fashion at −30°C, while the Zn-species thus formed undergo complete epimerization at +50°C. In a similar way, the Li/Cu transmetallation was examined. Thus, Li-species **2a** was treated successively with a THF mixture of CuCN and TMEDA (one equivalent each, −78°C, 1 h), Me_3SiCl (1 equivalent, 5 mm), and the propiolate (1 h) to afford 41% yield of 1,4-adduct (*R*)-**8a** in 83%ee (HPLC, Chiralcel AD), along with 17% of the dimeric product **9a** as an *E*/*Z* mixture (79:21); neither of **7a** nor the silylation product were obtained, indicating that the transmetallation was completed. Note that the formation of **9a** has been observed when Li-species **2a** was warmed up to +25°C [2]. The (*R*)-configuration of adduct **8a** was assigned after its conversion to (*R*)-(+)-4-phenyl-l,2-butanediol (via ozonolysis followed by reduction with $NaBH_4$) which was correlated with an authentic (*R*)-(+)-isomer obtained by DIBAL-H reduction of (*R*)-2-hydroxy-4-phenylbutanoic acid. Since the 1,4-addition step is likely to proceed in a retentive manner [10,11], this outcome strongly suggests that the Li/Cu transmetallation proceeds predominantly, but not completely, with retention of configuration, although the inversion/inversion pathway cannot be completely excluded. The high stereospecificity observed here is in sharp contrast to Linderman's observation [11] that a similar Li/Cu transmetallation of α-(methoxymethoxy)alkyllithium (configurationally stable!) followed by 1,4-addition onto the propiolate resulted in considerable racemization. Anyway, the chiral Cu-species thus generated is configurationally less stable than other organometallic species examined in this work.


(*S*)-**7a**, P =Cb
(*S*)-**7a'**, P=(*R*)-MTPA


(*R*)-**8a**


9a, R=$PhCH_2CH_2$

Finally, we examined the transmetallations on the chiral Li-species **11** (an analogue of Hoppe's Li-species **5** [5]) generated from enantiopure (*R*)-α-methylbenzyl *N*,*N*-diethylcarbamate (**10**) with *s*-BuLi/TMEDA in ether at −78°C. By analogy, **11** should be configurationally stable as well. Indeed, simple deuteration of **11** with MeOD gave (*R*)-**12** in 84%ee, as determined after its conversion to the MTPA ester **12'** in the same way as described for (*S*)-**7a**. Successive treatment of **11** with $MgBr_2$ at −78°C for 5 min and MeOD was found to give (*R*)-**12** in 83%ee, suggesting that the Li/Mg transmetallation proceeds in a highly retentive fashion. By contrast, a similar transmetallation with $ZnBr_2$ provided (*R*)-**12** in much lower ee's (6–43%), varying with the reaction conditions. This observation is best interpreted as a result that the Li/Zn transmetallation affords a mixture of invertive and retentive processes, although the possibility that the Zn-species thus formed is configurationally labile cannot be totally excluded [9].


(*R*)-**10**, X=H, P=$CONEt_2$; **11**, X=Li, P=$CONEt_2$
(*R*)-**12**, X=D, P=$CONEt_2$; **12'**, X=D, P=(*R*)-MTPA

In summary, we have elucidated the steric courses of several transmetallation processes on the enantiomerically defined, configurationally stable α-carbamoyloxy alkyllithiums. Although most of the stereochemical outcomes thus observed are what one might anticipate and the organolithiums studied in this work are rather special in type, the observations outlined herein provide unique and useful insights into the stereochemical aspect of transmetallation processes and the configurational stabilities of organometallic species involved therein.

Acknowledgements

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References

[1] For the recent progress in chemistry of enantio-enriched α-carbamoyloxy organolithiums: D. Hoppe, T. Hense, Angew. Chem. Int. Ed. Engl. 36 (1997) 5531.
[2] K. Tomooka, H. Shimizu, T. Inoue, H. Shibata, T. Nakai, Chem. Lett. (1999) 759. Cf. H. Shimizu, Masters Thesis, Tokyo Institute of Technology, 1999.
[3] (a) W.C. Still, C. Sreekumar, J. Am. Chem. Soc. 102 (1980) 1202. (b) J.S. Sawyer, A. Kucerovy, T.L. Macdonald, G.J. McGarvey, J. Am. Chem. Soc. 110 (1988) 842. (c) K. Tomooka, H. Yamamoto, T. Nakai, Liebigs Ann./Recueil (1997) 1275, and references cited therein.
[4] D. Hoppe, F. Hintze, P. Tebben, Angew. Chem. Int. Ed. Engl. 29 (1990) 1422.
[5] Carstens, D. Hoppe, Tetrahedron 50 (1994) 6097 (and their earlier papers cited therein).
[6] R.W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, Angew. Chem. Int. Ed. Engl. 39 (2000) 3072.
[7] G.J. McGarvey, M. Kimura, J. Org. Chem. 47 (1982) 5422.
[8] K. Tomooka, N. Komine, T. Sasaki, H. Shimizu, T. Nakai, Tetrahedron Lett. 39 (1998) 9715.
[9] (a) S. Klein, I. Marek, J.-F. Normant, J. Org. Chem. 59 (1994) 2925. (b) S. Norsikian, I. Marek, S. Klein, J.F. Poisson, J.-F. Normant, Chem. Eur. J. 5 (1999) 2055. (c) I. Marek, J. Chem. Soc. Perkin Trans. 1 (1999) 535.
[10] T. Tomoyasu, K. Tomooka, T. Nakai, Tetrahedron Lett. 41 (2000) 345 (and references cited therein).
[11] (a) R.J. Linderman, B.D. Griedel, J. Org. Chem. 56 (1991) 5491. (b) R.J. Linderman, B.D. Griedel, J. Org. Chem. 55 (1990) 5428.