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Asymmetric synthesis of enantio-enriched acyclic α-amino alkylstannanes and rearrangement behavior of carbanions thereof

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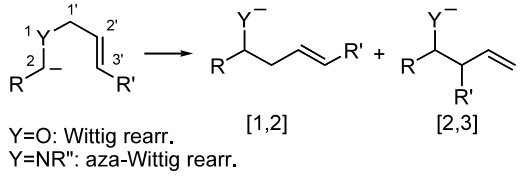
Abstract—An efficient stereocontrolled synthesis of enantio-enriched *N*-Boc-*N*-allyl-α-amino alkylstannanes and *N*,*N*-diallylic α-amino alkylstannanes starting from enantio-enriched α-hydroxy alkylstannane has been developed. The aza-Wittig rearrangement of enantio-defined *N*,*N*-diallyl-α-amino alkyllithium, generated by tin–lithium exchange, is shown to proceed predominantly with inversion of configuration at the Li-bearing carbon terminus. © 2003 Elsevier Science Ltd. All rights reserved.

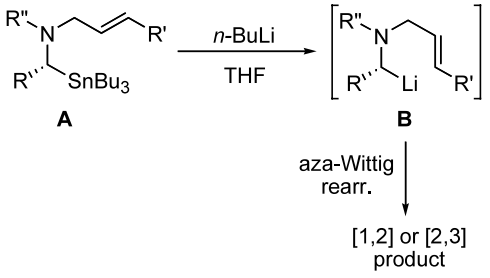
The Wittig rearrangement of allyl ether systems (Scheme 1, Y = O), particularly its asymmetric version using enantio-enriched substrates, has enjoyed widespread application in stereocontrolled synthesis.[1] In contrast, despite its potential utility, the aza-Wittig rearrangement (Scheme 1, Y = NR″) is far less exploited in asymmetric synthesis because of the considerable difficulty encountered in the generation of enantio-enriched α-amino carbanions.[2] In their pioneering work, Gawley and co-workers have reported the aza-Wittig rearrangement of (*R*)-*N*-allyl-2-lithiopyrrolidine, generated by a tin-lithium transmetalative protocol,[3] which affords the aza-Wittig product in moderate enantiomeric purity.[4] However, no aza-Wittig rearrangement of acyclic α-amino alkylstannanes, initiated by tin–lithium exchange, has been reported yet except for the examples of primary α-amino methylstannane systems.[5] We now report a new efficient synthetic approach to acyclic enantio-enriched *N*,*N*-disubstituted α-amino alkylstannanes **A** and our preliminary results of the aza-Wittig rearrangement thereof, which involves an enantio-defined α-amino alkyllithium **B** generated by tin–lithium exchange (Scheme 2).

As a substrate for this rearrangement, initially we chose *N*-allylic α-amino alkylstannanes which contained a Boc group on nitrogen to stabilize the configuration of the resulting α-amino carbanion due to its coordination effect.[6] While the preparation of this class of compounds, i.e. α-amino alkylstannanes, had so far been tedious,[7] at first we examined improvement of its synthetic route from easily available α-hydroxy alkylstannane (*S*)-**1**[8] via mesylation followed by the S_N2 reaction with amino reagents (Scheme 3).[9,10]

As the result, the required *N*-allyl aminostannane (*R*)-**2** (>95% ee) was obtained in 65% overall yield from α-hydroxy phenylpropylstannane (*S*)-**1** (>95% ee) without loss of stereochemical integrity.[11,12] The key feature of this method is the high degree of inversion of



Scheme 1.



Scheme 2.

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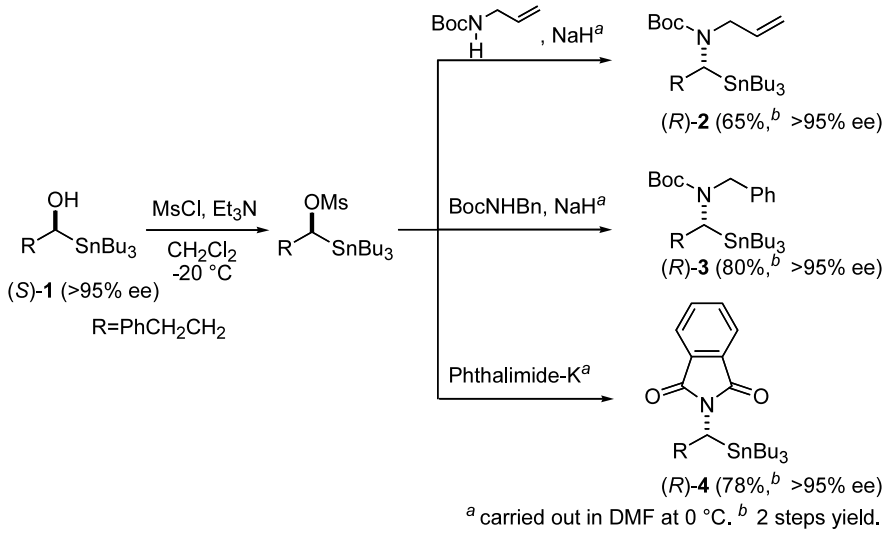
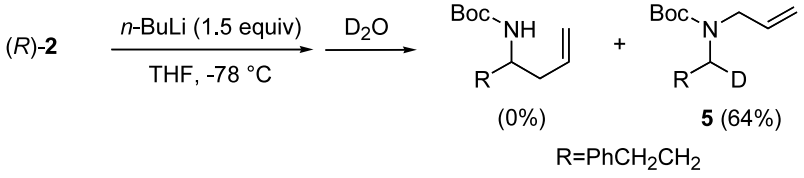


Scheme 3.

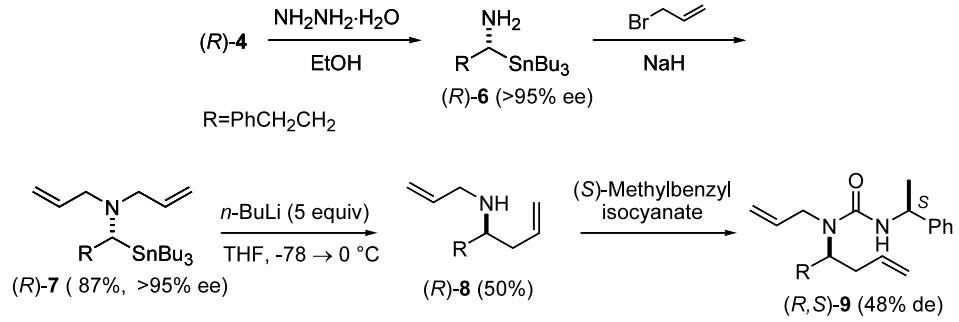
configuration in the S_N2 process. Similar reactions using *N*-Boc-benzylamine and phthalimide provide the corresponding stannane (*R*)-**3** and (*R*)-**4** as an enantiopure form, respectively.[11,13] Next, we examined the transmetalative rearrangement of the thus-obtained (*R*)-**2**. However, disappointingly, reaction of (*R*)-**2** with *n*-BuLi provided neither [1,2]- nor [2,3]-Wittig rearrangement product, and, instead, deuterated product **5** was obtained by quenching with D_2O at that temperature (Scheme 4).[14]

This result suggests that the Boc-protected α-amino alkyllithium thus generated is still not reactive enough to undergo the aza-Wittig rearrangement, probably due to the remarkable dipole stabilization of the α-amino carbanion. These observations prompted us to redesign the rearrangement system for a non-Boc substituted one. The requisite stannane (*R*)-**7** was prepared from phthalimide derived (*R*)-**4** via reaction with hydrazine hydrate followed by bis-allylation.[15] Reaction of *N*,*N*-diallyl aminostannane (*R*)-**7** with *n*-BuLi was found to afford the desired aza-Wittig rearrangement product **8** in 50% yield (Scheme 5).[16,17] The absolute stereochemistry and enantiopurity of **8** was determined to be 48% ee (*R*) by the HPLC analysis of its (*S*)-methylbenzyl urea derivative **9**.[18]

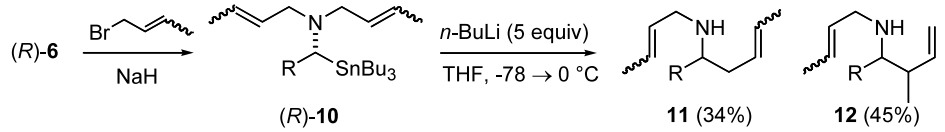
Since tin–lithium exchange proceeds with retention of configuration,[19] it appears that the rearrangement proceeds predominantly with inversion at the Li-bearing carbon terminus. While a complete explanation of the loss of enantiospecificity is not possible at present, it might be taken into account that the α-amino alkyllithium intermediate might be configurationally labile



Scheme 4.



Scheme 5.



Scheme 6.

and/or aza-Wittig rearrangements would proceed with low stereospecificity. Furthermore, a similar reaction of (*R*)-**10** (*E*/*Z* mixture) was found to afford a mixture of [1,2]-rearrangement product **11** and [2,3]-rearrangement product **12**, which means that this class of rearrangement proceeds with low periselectivity (Scheme 6).[20]

In summary, we have developed a convenient method for the preparation of enantio-enriched *N*-Boc-*N*-allyl-α-amino alkylstannanes and *N*,*N*-diallylic α-amino alkylstannanes from enantio-enriched α-hydroxy alkylstannane. Furthermore, we have demonstrated that the first example of aza-Wittig rearrangement of acyclic enantio-enriched *N*,*N*-diallylic α-amino alkylstannanes via tin-lithium exchange proceeds predominantly with inversion of configuration at the lithium-bearing carbon terminus. Further work is in progress to elucidate the mechanism of this rearrangement and to enhance the synthetic potential thereof.

Acknowledgements

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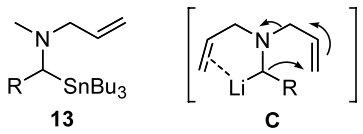
References

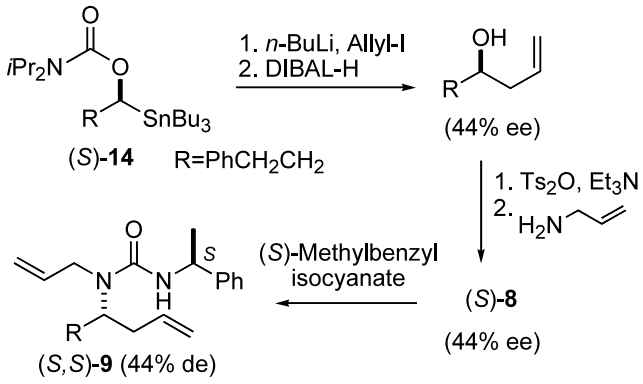
1. Reviews: (a) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, pp. 975–1014; (b) Nakai, T.; Mikami, K. *Org. React*. **1994**, *46*, 105–209; (c) Nakai, T.; Tomooka, K. *Pure Appl. Chem*. **1997**, *69*, 595–600.
2. Review: Vogel, C. *Synthesis* **1997**, 497–505.
3. A tin–lithium transmetalative method provides easy access to configurationally stable α-amino alkyllithiums: (a) Chong, J. M.; Park. S. B. *J. Org. Chem*. **1992**, *57*, 2220–2222; (b) Burchat, A. F.; Chong, J. M.; Park. S. B. *Tetrahedron Lett*. **1993**, *34*, 51–54; (c) Gawley, R. E.; Zhang, Q. *J. Org. Chem*. **1995**, *60*, 5763–5769.
4. Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc*. **1995**, *117*, 11817–11818.
5. (a) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem*. **1974**, *66*, 209–217; (b) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275–1276.
6. The first synthesis of *N*-allyl-*N*-Boc-α-amino alkylstannane was reported by Chong's group. However, they have not commented on the aza-Wittig rearrangement thereof, see: Ref. 3a.
7. A wide variety of methods have been reported for the preparation of acyclic α-amino alkylstannanes but all give primary or racemic products. (a) Peterson, D. J. *J. Am. Chem. Soc*. **1971**, *93*, 4027–4031; (b) Quintard, J.-P.; Elissondo, B.; Jousseaume, B. *Synthesis* **1984**, 495–498; (c) Elissondo, B.; Verlhac, J.-B.; Quintard, J.-P.; Pereyre, M. *J. Organomet. Chem*. **1988**, *339*, 267–275; (d) Ahlbrecht, H.; Baumann, V. *Synthesis* **1994**, 770–772; (e) Pearson, W. H.; Stevens, R. P. *Synthesis* **1994**, 904–906; (f) Katritzky, A. R.; Chang, H.-X.; Wu, J. *Synthesis* **1994**, 907–908; (g) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Org. Chem*. **1996**, *61*, 7627–7630.
8. (a) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett*. **1988**, *29*, 1657–1660; (b) Chan, C. M.; Chong, J. M. *J. Org. Chem*. **1988**, *53*, 5584–5586; (c) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett*. **1994**, *35*, 1913–1916.
9. Chong's group has reported that enantio-enriched α-phthalimido alkylstannane can be prepared by the Mitsunobu reaction of enantio-enriched α-hydroxy alkylstannane and phthalimide, see: Ref. 3a.
10. The S_N2 reaction with alkoxides has been reported: Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett*. **1993**, *34*, 8139–8142.
11. The enantiopurity of (*R*)-**2**,**3** was determined by chiral HPLC analysis (Chiralcel OD-H, 0.46×25 cm).
12. All the compounds were characterized by ^1H and ^{13}C NMR analysis. Data for selected products are as follows. (*R*)-**2**: ^1H NMR ($CDCl_3$) δ 0.80–0.95 (m, 15H), 1.24–1.58 (m, 12H), 1.43 (s, 9H), 2.00–2.15 (m, 2H), 2.50–2.65 (m, 2H), 2.92–3.00 (m, 1H), 3.54 (dd, $J=7.4$, 15.0 Hz, 1H), 4.03 (dd, $J=5.8$, 15.0 Hz, 1H), 5.05–5.13 (m, 2H), 5.70–5.85 (m, 1H), 7.16–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 10.6, 13.7, 27.6, 28.5, 29.2, 34.6, 34.9, 49.0, 53.8, 79.0, 116.6, 125.7, 128.3, 128.3, 135.0, 142.3, 155.4. $[\alpha]_D^{25}$ +10.5° (*c* 1.0, $CHCl_3$). (*R*)-**3**: ^1H NMR ($CDCl_3$) δ 0.80–0.95 (m, 15H), 1.19–1.52 (m, 12H), 1.46 (s, 9H), 2.00–2.11 (m, 2H), 2.45–2.55 (m, 2H), 2.81–2.87 (m, 1H), 4.07 (d, $J=15.0$ Hz, 1H), 4.67 (d, $J=15.0$ Hz, 1H), 7.06–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 10.6, 13.7, 27.5, 28.5, 29.1, 31.6, 34.4, 48.8, 53.3, 79.3, 125.7, 127.2, 127.8, 128.2, 128.3, 128.7, 138.8, 142.2, 155.5. $[\alpha]_D^{25}$ +17.6° (*c* 0.25, $CHCl_3$). (*R*)-**4**: ^1H NMR ($CDCl_3$) δ 0.81–1.53 (m, 27H), 1.95–2.09 (m, 1H), 2.28–2.43 (m, 1H), 2.59 (t, $J=7.8$ Hz, 2H), 4.04 (dd, $J=5.6$, 10.2 Hz, 1H), 7.05–7.25 (m, 5H), 7.65–7.69 (m, 2H), 7.75–7.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 10.3, 13.6, 27.3, 28.9, 34.6, 34.9, 37.4, 122.8, 125.6, 128.2, 132.0, 133.6, 141.4, 169.1. $[\alpha]_D^{25}$ +76.0° (*c* 1.0, $CHCl_3$). (*R*)-**7**: ^1H NMR ($CDCl_3$) δ 0.81–0.91 (m, 15H), 1.24–1.52 (m, 12H), 1.72–1.86 (m, 1H), 2.02–2.19 (m, 1H), 2.47–2.60 (m, 1H), 2.63 (dd, $J=14.0$, 7.3 Hz, 2H), 2.81–2.95 (m, 1H), 3.09 (dd, $J=10$,2, 5.4 Hz, 1H), 3.29 (dd, $J=14.0$, 4.8 Hz, 2H), 5.05–5.19 (m, 4H), 5.81 (dddd, $J=17.0$, 10.2, 7.3, 4.8 Hz, 2H), 7.16–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 10.6, 13.6, 27.6, 29.4, 34.8, 35.2, 57.0, 57.5, 116.4, 125.5, 128.2, 128.5, 137.6, 142.9. $[\alpha]_D^{25}$ −60.0° (*c* 0.25, $CHCl_3$). (*R*)-**8**: ^1H NMR ($CDCl_3$) δ 1.69–1.77 (m, 2H), 2.17–2.31 (m, 2H), 2.63–2.69 (m, 3H), 3.23 (dd, $J=5.9$, 1.3 Hz, 2H), 5.04–5.18 (m, 4H), 5.74–5.93 (m,

2H), 7.17–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 32.0, 35.6, 38.3, 49.6, 55.5, 115.7, 117.4, 125.7, 128.3, 128.3, 135.4, 137.2, 142.5. (*R*)-**10** (major diastereomer): ^{1}H NMR ($CDCl_3$) δ 0.81–0.91 (m, 15H), 1.24–1.73 (m, 18H), 1.75–1.90 (m, 1H), 2.09–2.22 (m, 1H), 2.49–2.65 (m, 3H), 2.81–2.95 (m, 1H), 3.10–3.31 (m, 3H), 5.40–5.63 (m, 4H), 7.16–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 10.7, 13.7, 17.8, 27.6, 29.4, 34.8, 35.0, 50.8, 56.6, 125.5, 127.4, 128.2, 128.6, 130.2, 143.0. **11** (major diastereomer): ^{1}H NMR ($CDCl_3$) δ 1.55–1.69 (m, 8H), 2.13–2.17 (m, 2H), 2.54–2.61 (m, 3H), 3.07–3.20 (m, 2H), 5.34–5.54 (m, 4H), 7.07–7.23 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.1, 17.8, 31.3, 32.1, 35.7, 49.1, 56.5, 125.7, 125.9, 126.3, 127.0, 128.3, 128.3, 129.8, 142.6. **12** (major diastereomer): ^{1}H NMR ($CDCl_3$) δ 1.03–1.08 (m, 3H), 1.62–1.90 (m, 5H), 2.41–2.52 (m, 2H), 2.55–2.85 (m, 2H), 3.17–3.30 (m, 2H), 5.07–5.13 (m, 2H), 5.51–5.84 (m, 3H), 7.18–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15.5, 17.7, 32.6, 32.8, 40.3, 49.6, 60.5, 114.8, 125.6, 126.9, 128.3, 128.3, 130.0, 141.9, 142.8.

13. The enantiopurity of (*R*)-**4** was determined by ^{1}H NMR analysis after conversion (hydrazine hydrate/MTPACl) to a MTPA amide of (*R*)-**6**.
14. Treatment of (*R*)-**2** with *n*-BuLi at −78→0°C led to complex mixtures of products.
15. Unfortunately, a previously developed synthetic method from (*S*)-**1** was not applicable to the preparation of diallyl derivatives.
16. The intramolecular coordination between the lithium and the olefinic π-bond may play a very important role for configurational stability of α-amino alkyllithiums, see: Komine, N.; Tomooka, K.; Nakai, T. *Heterocycles* **2000**, *52*, 1071–1074.
17. In contrast, a similar reaction of *N*-allyl-*N*-Me-α-amino alkylstannane **13** gave no rearrangement product. Thus, the reasonable coordination ability of the olefinic π-bond in the transition state **C** appears to be well suited for aza-Wittig rearrangement.



18. Authentic samples of (*S*)-**8** and (*S*,*S*)-**9** were prepared as depicted below. The starting stannane (*S*)-**14** (>95% ee) was prepared by our reported method, see: Tomooka, K.; Shimizu, H.; Inoue, T.; Shibata, H; Nakai, T. *Chem. Lett.* **1999**, *1*, 759–760.



19. Retention of stereochemistry in tin–lithium exchange reactions is well-known for the preparation of stereochemically defined α-hetero alkyllithiums, see: Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622–2636 and references cited therein.
20. Rearrangement products **11** and **12** were obtained as a complex mixture of several diastereomers. Thus, the enantiopurity of the products has not yet been determined.