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Configurational and Conformational Effects on Tin−Lithium Exchange in α-Aminoorganostannanes by Rapid-Injection NMR

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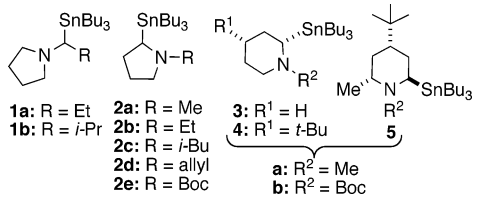
Four recent monographs attest to the importance of organolithium compounds in organic synthesis.[1] As a class of functionalized organolithiums, α-aminoorganolithiums have proven to be very popular as intermediates in numerous synthetic applications.[2] They react with a wide variety of electrophiles to give products of electrophilic substitution (S_E2) in excellent yield. Additionally, α-aminoorganolithiums undergo stereoselective rearrangements, cycloadditions, and anionic cyclizations to give a wide variety of elaborated products. Moreover, transmetalation from lithium to magnesium or a transition metal affords species with reactivity profiles that complement those of the organolithium.

While the simplest method of preparation of α-aminoorganolithiums is deprotonation, this method has limitations, including a lack of regiospecificity and a high kinetic barrier. Deprotonation α to an amine nitrogen is usually, but not always,[3] only possible for compounds where the nitrogen lone pair is delocalized into a nitroso, carbonyl, or azomethine[4] or quaternized.[5] The former produce dipole-stabilized organolithiums, the latter afford nitrogen ylides. Unstabilized α-aminoorganolithiums lacking such stabilization are available by tin−lithium exchange.[6,7]

The tin−lithium exchange reaction is occasionally unpredictable, appearing facile in some situations, and impossible in apparently similar compounds. For example, tin−lithium exchange fails with **1a**[8] and **1b**[9] but is facile for **2a**−**e**.[7,10] Piperidines **3a** and **4a** undergo transmetalation readily, whereas **5a** is unreactive.[11] The relevant difference between piperidines **4a** and **5a** is the configuration of the tin relative to the *tert*-butyl group at carbon 4.



The reason for the failure of **1a,b** to transmetalate is thermodynamic:[12] the corresponding α-aminoorganolithium is less stable than BuLi, so it cannot be eliminated from an intermediate stannate complex.[9,13] In this paper, we report kinetic studies of the tin−lithium transmetalation, at 191 K, of **2a**, **2e**, and **3**−**5**. These studies reveal the influence of ring size, conformation, and configuration on the rate of transmetalation. Our studies were conducted using the rapid-injection NMR technique (RINMR), which was originally developed using proton observation.[14] We are not aware of prior RINMR studies using ^{119}Sn.

Longitudinal relaxation times for the ^{119}Sn nuclei in piperidines **3a**, **4a**, and **5a** are in the range of 3.8−6.6 s (see Supporting Information). To ensure accurate integration, repetition time between 30° pulses in the RINMR experiment was set at 20 s. Tetra(isopropyl)tin, Sn(*i*-Pr)$_4$, was chosen as an internal standard since it is inert under the reaction conditions.

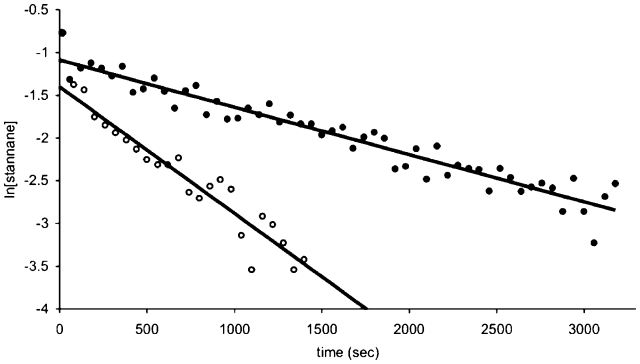
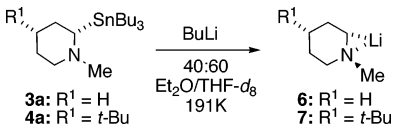


Figure 1. First-order plot of the disappearance of **3a** (closed circles) and **4a** (open circles) at 191 K. Each data point is the average of three successive integrals taken at 20 s intervals. For **3a**, the integral of the two conformers was summed.

Scheme 1



Exploratory studies indicated that solvent effects are significant. When the transmetalation of **3a** was carried out in d_8-THF by injection of a solution of BuLi in ether, the reaction was too fast for the rapid injection technique (i.e., the reaction was over in less than 20 s). Conversely, the same experiment in diethyl ether was too slow to be practical (several hours). A 40:60 mixed solvent of Et_2O/THF-d_8 was used to effect tin−lithium exchange in times compatible with the RINMR technique using ^{119}Sn NMR. Even so, some of the tested substrates underwent transmetalation at rates too fast for RINMR in this solvent mixture (see below). An example of the experimental results are illustrated by the transmetalation of **3a**/**4a** to **6**/**7** (Scheme 1).

While the initial spectra were broadened by mixing and a small exotherm, line shape in subsequent spectra was excellent. Spectra from a typical RINMR experiment are shown in the Supporting Information. Excellent kinetic fits were obtained by monitoring the disappearance of stannane. The first-order plot of the disappearance of **3a** and **4a** is shown in Figure 1. Similar plots are in the Supporting Information. Pyrrolidines **2a** and **2e** were consumed in <20 s under similar conditions, the latter even in pure ether or hexane/ether mixed solvent. Good spectra of stannylpiperidine **3b** at 191 K were not possible due to dynamic line broadening, but **3b** was also consumed in <20 s in ether/THF. The observed first-order rate constants for transmetalation of these compounds are listed in Table 1. For comparison, k_{obs} values for **2a**, **2e**, and **3b** are estimated as $>6.9 \times 10^{-2}$ s^{-1} based on a conservatively estimated half-life of ≤10 s.

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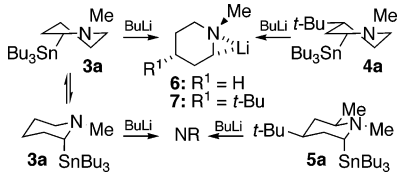
Table 1. Observed and Estimated First-Order Rate Constants for the Transmetalation of α-Aminoorganostannanes at 191 K

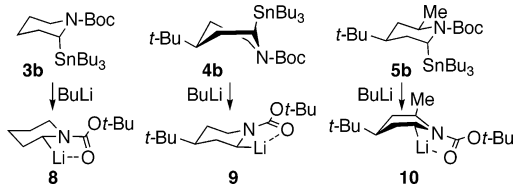
stannane	solvent	$k_{obs} \times 10^{-4}$ s^{-1}
2a	40:60 ether/THF	>690[a]
2e	ether	>690[a]
2e	ether/hexane	>690[a]
3a	40:60 ether/THF	5.4 ± 0.2
3b	40:60 ether/THF	>690[a]
4a	40:60 ether/THF	14.8 ± 0.1
4b	40:60 ether/THF	7.8 ± 0.6
5a	40:60 ether/THF	0.3 ± 0.09
5b	40:60 ether/THF	1.4 ± 0.09

[a] Estimated based on $t_{1/2} \leq 10$ s.

Scheme 2



Scheme 3



Using the Karplus-like relationship of ^3J ^{13}C−^{119}Sn coupling constants of *N*-methyl stannylpiperidines,[15] the conformation of **4a** and one of the conformational isomers of **3a** have previously been shown to be half-chairs, with the nitrogen lone pair and the C2−Sn bond in a synperiplanar orientation (Scheme 2). In contrast, **5a** and the other conformation of **3a** are chairs having the C−Sn bond antiperiplanar to the nitrogen lone pair.[13] Although piperidine **4a** transmetalates readily, axial stannane **5a** shows no appreciable transmetalation at −78 °C after 45 min in THF.[11] In 40:60 ether/THF, a small amount of transmetalation is observed over 35 min, giving relative rates for tin−lithium exchange of **4a**/**5a** of between 40:1 and 70:1. The two conformations of **3a** are nearly equally populated.[16] The observed rate for transmetalation of conformationally mobile stannane **3a** is intermediate between the rates for **4a** and **5a**, consistent with Winstein−Holness kinetics,[17] in which only one conformer of **3a** is reactive toward transmetalation.

A different situation is observed in the relative rates of *N*-Boc stannylpiperidines **3b**, **4b**, and **5b** (Scheme 3): the mobile piperidine **3b** reacts 2−3 orders of magnitude faster than either of the conformationally locked piperidines **4b**/**5b**. Conformational effects may also influence the relative rates of the transmetalation of **3b**, **4b**, and **5b**, as shown in Scheme 3. Due to $A^{1,3}$ strain, the C−Sn bond is orthogonal to the Boc group, which forces the tin axial in **3b** and the ring of **4b** into a twist boat. In the lithium compounds **8**−**10**, the C−Li bond is in the nodal plane of the amide, and the lithium is coordinated to the carbonyl oxygen. When **4b** transmetalates, the ring can relax into chair conformation **9**, whereas when **5b** transmetalates, twist-boat **10** is formed.

Interestingly, pyrrolidines **2a** and **2e** undergo transmetalation at rates too fast for the RINMR technique, independent of solvent. Given the conformational effects observed in the piperidine series, the possibility of conformational mobility due to pseudorotation in the five-membered rings may be at least partly responsible for the accelerated transmetalation of the stannylpyrrolidines.

In summary, we have found that configurational and conformational effects can play a role in the rate of tin−lithium exchange in α-aminoorganolithiums, in addition to the well-established thermodynamic effects.

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Supporting Information Available: General experimental procedures, NMR data and spectra, and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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