Asymmetric Synthesis of Tertiary Alcohols and Thiols via Nonstabilized Tertiary α-Oxy- and α-Thio-Substituted Organolithium Species

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Abstract: Nonstabilized α-O-substituted tertiary organolithium species are difficult to generate, and the α-S-substituted analogues are configurationally unstable. We now report that they can both be generated easily and trapped with a range of electrophiles with high enantioselectivity, providing ready access to a range of enantioenriched tertiary alcohols and thiols. The configurational stability of the α-S-organolithium species was enhanced by using a less coordinating solvent and short reaction times.

Chiral α-heteroatom (O, N, and S)-substituted organolithium compounds are a versatile class of nucleophiles that are useful in the asymmetric synthesis of chiral alcohols, amines, and thiols.[1] Although the use of secondary and mesomerically stabilized (e.g., benzylic and allylic) tertiary α-O- and α-S-substituted organolithium reagents in synthesis is well established,[1a–c] the use of non-mesomerically stabilized (i.e., dialkyl-substituted) tertiary reagents is not. This discontinuity is due to contrasting problematic features governing α-O- and α-S-substituted organolithium species. Nonstabilized tertiary α-O-organolithium compounds are configurationally stable but are difficult to generate owing to their reduced kinetic acidity (Scheme 1B).[1c–e] Tertiary α-S-organolithium species are easily formed but are not configurationally stable (Scheme 1A). To apply α-O/S-substituted organolithium compounds in asymmetric synthesis, both ease of generation and configurational stability are essential requirements.[1a–d,3]

Through variation of the directing group, base, solvent, and additives we discovered reaction conditions enabling the stereospecific deprotonation of secondary dialkyl benzoates (TIB esters)[4] and demonstrated their configurational stability in lithiation–borylation reactions.[5] Herein, we report the broad applicability of these novel enantioenriched nucleophiles in reactions with a broad range of electrophiles. In addition, we have discovered reaction conditions for the generation of enantioenriched, tertiary, nonstabilized α-S-organolithium compounds and report their subsequent trapping with electrophiles in high enantioselectivity (Scheme 1C).

Boronic esters represent a niche class of electrophiles,[6] and therefore, we initially embarked on a study of the trapping of tertiary α-O-substituted organolithium species, which were generated by lithiation of the enantioenriched TIB esters 1a–1e, with a range of electrophile classes (Scheme 2). Upon exposure of a variety of enantioenriched benzoates to sec-BuLi and TMEDA in CPME at −60 °C, the corresponding organolithium species Li-1a–1e were generated. Pleasingly, Li-1a–1e were successfully trapped with a range of electrophiles, including methyl chloroformate (2aa), benzoyl chloride (2ab), isocyanates (2ac and 2ad), aldehydes (2ae and 2af), and trialkyl tin chlorides (2ag, 2ah, 2ba–2ca). Reactions with aldehydes gave mixtures of diastereomers (see 2ae and 2af) but in the case of PhCHO, high...
Diastereoselectivity was observed (11:1 d.r.). In all cases, the desired tertiary alcohol derivatives were obtained in good to high yields and, importantly, with universally complete enantioselectivity and retention of configuration, as determined by X-ray crystallographic analysis of \( \text{2ad} \) and \( \text{2af} \) (see the Supporting Information). In addition, the TIB group could be easily removed upon reduction with LiAlH\(_4\) to give the tertiary alcohol \( \text{3} \).

Having demonstrated the scope of the electrophilic trapping of nonstabilized, tertiary \( \alpha \)-O-substituted organolithium species, we conducted studies to evaluate whether stannanes \( \text{2ag} \) and \( \text{2ah} \) could serve as bench-stable organolithium precursors by tin–lithium exchange (Scheme 3).\(^{[7]}\) However, treatment of the tributyltin derivative \( \text{2ag} \) with \( \text{n-BuLi} \) with or without TMEDA followed by quenching with CH\(_3\)OD only gave \([\text{D}]\)-\( \text{1a} \) with poor conversion, albeit with excellent stereoselectivity (with retention of configuration, see entries 1 and 2). In contrast, treatment of the less hindered trimethyltin derivative \( \text{2ah} \) with \( \text{n-BuLi/} \)TMEDA was much more successful and yielded \([\text{D}]\)-\( \text{1a} \) in excellent yield and with complete stereoselectivity and retention of configuration (entries 3 and 4), indicating that \( \text{2ah} \) could indeed serve as a useful precursor to the corresponding organolithium species.\(^{[9]}\)

An understanding of the configurational stability of chiral organolithium species is crucial for exploiting their use in synthesis.\(^{[3,9]}\) Interestingly, the tertiary \( \alpha \)-O-substituted organolithium species \( \text{Li-1} \) were found to be chemically and configurationally stable below –40°C but at higher temperatures, decomposition rather than racemization occurred. Similar observations have been made with secondary \( \alpha \)-O-substituted organolithium TIB esters whilst the corresponding carbamates are slightly more stable and only decompose above –20°C.\(^{[2b,7c,10]}\) All of these nonstabilized \( \alpha \)-O-organolithium species decompose before they racemize.

Having demonstrated the broad applicability of tertiary nonstabilized chiral \( \alpha \)-O-organolithium species, we then embarked on a study of the more challenging sulfur analogues.\(^{[1c,11]}\) Pioneering work by Beak had revealed that while the \( \alpha \)-deprotonation of dialkyl-substituted tertiary thiobenzoates (such as \( \text{4} \)) was facile at low temperature, they were configurationally unstable even at –98°C in THF (Scheme 1A).\(^{[12]}\)

Only tertiary or hindered, branched \( \alpha \)-S-substituted organolithium compounds (e.g., \( \text{5a–5e} \)) have been reported to be configurationally stable;\(^{[13]}\) all others are unstable (Scheme 4A).\(^{[14]}\) This can be explained based on the mechanism of racemization of \( \alpha \)-S-substituted organolithium compounds, which involves solvent separation of the ion pair, rate-determining rotation of the hyperconjugated C–S bond, and recombination of the ion pair (Scheme 4B).\(^{[15]}\) Thus configurational stability in \( \alpha \)-S-organolithium compounds is only observed with hindered substrates where there is a high barrier to C–S bond rotation. Given this observation, we proposed that nonstabilized, tertiary \( \alpha \)-S-substituted organolithium species derived from thiobenzoates \( \text{4} \) should be configurationally stable and therefore re-examined the conditions for lithiation.

Enantiomerically enriched thiobenzoates \( \text{4a} \), which were synthesized from the corresponding secondary alcohols and 2,4,6-trisopropylthiobenzoic acid by a Mitsunobu reaction,
were lithiated under a variety of reaction conditions and subsequently reacted with CH₂OD (Scheme 5). Using THF as the solvent gave the product [D]-4a as a racemate (entry 1), thus confirming Beak’s observations. Gratifyingly, the use of Et₂O as the solvent generated [D]-4a in 90:10 e.r. and complete conversion (entry 2). TMEDA was crucial to facilitate deprotonation as in its absence, [D]-4a was formed only in low yield (entry 3).[10] TMBE was found to be the most suitable solvent (entry 4), and even a very short deprotonation time (5 min) was sufficient to give the desired product [D]-4a with 100% conversion and 97:3 e.r. with retention of configuration (entry 5). These results show that the racemization of the tertiary α-S-substituted organolithium species can be minimized when less coordinating solvents and short reaction times are employed, reaction conditions that maintain a tight ion pair.

Having identified the most suitable reaction conditions for the α-deprotonation of STIB ester 4 and trapping with CH₂OD, we evaluated the scope of electrophiles that could be employed. The same range of electrophiles that were compatible with the lithiated OTIB esters Li-1a–1e were also successful in trapping nonstabilized, tertiary α-S-substituted organolithium species derived from 4a–4e, and gave the tertiary thiol derivatives 6 in good yield and very high enantiomeric selectivity in all cases with the exception of Si- and Sn-based electrophiles (6a–6g. Scheme 6; see below). In the case of ClSnMe₂ (6ag), the predominant enantiomer arose from retentive addition to the organolithium (S₉2ret), whereas for ClSnBu₃ (6af), inversion was observed (S₉2inv).[17]

We extended the method further by preparing the STIB cholesterol derivative 8, which upon exposure to the optimized reaction conditions gave 9 (CICO₂Me quench) in excellent yield and as a single diastereoisomer (Scheme 7).[18] This example highlights two key features in the generation of nonstabilized, tertiary α-S-substituted organolithium intermediates under our conditions. 1) Although the Li atom adopts an equatorial position in Li-8, an orientation that according to Beak[13] and Reich[15] will favor epimerization by forming the more stable configuration with an axially positioned lithium (where the bulky TIB group is placed at an equatorial position), epimerization was not observed, underscoring the remarkable configurational stability of nonstabilized tertiary α-S-substituted organolithium species generated under our conditions. 2) The kinetic acidity of the α-S-proton in STIB esters 4 and 8 is remarkably high and outcompetes the lithiation of the allylic position.

To place these newly reported nonstabilized, enantioenriched tertiary α-S-substituted organolithium species on firmer foundations, we determined the thermodynamic parameters, ΔH° and ΔS°, of racemization.[19] Initial studies by Hoffmann and co-workers identified values of ΔG°[rac] = −78 kcal mol⁻¹ and ΔG°[rac] = −13 kcal mol⁻¹ for the racemization of 10b and 11b, respectively (Scheme 8A).[16][16] As previous studies were conducted on the S-Ph and S-duryl substrates 10 and 11, we performed kinetic studies on model compound Li-4a. Thus, lithiation of STIB 4a, followed by equilibration at −78, −70, −65, or −60°C, followed by cooling to −78°C, and quenching with
p-Br-C,H₃-NCO gave carbamate 6ab with different levels of enantioenrichment (see the Supporting Information). The erosion of e.r. observed in these experiments gave rise to an Eyring plot from which the parameters ΔΗ° and ΔS° were determined to be +13 kcal mol⁻¹ and -14 cal mol⁻¹, respectively[20] (Scheme 8B). This equates to a ΔG° former value of +10 kcal mol⁻¹, which is in line with Hoffmann’s results. Aside from providing the thermodynamic parameters for racemization, these studies also showed that racemization of Li-4 occurred at -78°C over an extended period of time, which is in contrast to the behavior of oxygen analogues Li-1, which do not racemize.

Finally, we decided to investigate the factors that are responsible for the low selectivity observed in the reaction of nonstabilized, tertiary α-S-substituted organolithium species with Si- and Sn-based electrophiles (Scheme 6, 6ae-ag). We speculated that a slow electrophilic quench might have resulted in partial racemization of Li-4 and therefore monitored the reaction by in situ IR spectroscopy (Scheme 9).[22,23] With the test electrophile CICO₂Me, where high e.r. values were observed, the in situ IR studies revealed that both lithiation of 4a and subsequent electrophilic quenching were extremely rapid at -78°C.

In the case of Me₂SiCl, the electrophilic trapping was slow with only 50% of the organolithium compound quenched after 1 h, thus leaving time for competing racemization.[24] However, in the case of the Bu₂SnCl and Me₂SnCl electrophiles (6af and 6ag), where poor e.r. values were observed, the IR profile revealed that quenching of Li-4a was rapid, as in the case of CICO₂Me. This excluded racemization of Li-4a as the sole cause of the poor e.r. observed. These unusual findings can be rationalized on the basis of competing retentive (S_r,2ret) and invertive (S_r,2inv) electrophilic substitution pathways in the quenching of Li-4a with tin electrophiles,[25] where the more hindered Bu₂SnCl electrophile favors the invertive pathway.

In conclusion, we have found that difficult-to-generate, nonstabilized, tertiary, α-O-substituted lithiated secondary dialkyl benzoates (OTIB esters) and previously regarded as configurationally unstable α-S-substituted lithiated secondary dialkyl thiobenzoates (STIB esters) can be generated, and are configurationally stable. Key to success in both cases was the use of mildly coordinating solvents together with TMEDA to enable deprotonation and, in the case of the α-S-organolithium species, short reaction times. The subsequent trapping of these rare, nonstabilized tertiary organolithium intermediates with electrophiles proceeded with excellent enantioselectivity, enabling the synthesis of highly enantioenriched tertiary alcohol and tertiary thiol derivatives. Therefore, we have established a new class of organolithium reagents for asymmetric synthesis.

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Conflict of interest

The authors declare no conflict of interest.

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[17] The absolute configurations of 6af and 6ag were determined after tin–lithium exchange and protonation and comparison of the HPLC traces with that of authentic STIB 4a.

[18] The absolute stereochemistry of 9 was determined by NMR spectroscopy. See the Supporting Information for details.


[21] The positive ΔS° value might result from reorganization of the solvent during a conducted-tour-like mechanism (see Refs. [1a] and [9]) where the lithium cation is escorted by the TIB group to the opposite face of the carbonyl.


[23] See the Supporting Information for the complete in situ IR traces, showing the carbonyl bands of 4a (1680 cm⁻¹), Li-4a (1585 cm⁻¹), and the products 6 (ca. 1637 cm⁻¹).

[24] In addition, slow quenching was also evident from the slow dissipation of the orange color of Li-4a, whereas the color dissipated rapidly with all other electrophiles. Facial selectivity may also contribute to the reduced e.r. observed with C5SiMe5.

[25] Different levels of facial selectivity have been observed in the electrochemical quenching of lithiated benzylic thiacarbamates; see Ref. [13c].