Chiral Alkyllithium Compounds

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Diastereoselective Synthesis of Open-Chain Secondary Alkyllithium Compounds and Trapping Reactions with Electrophiles**

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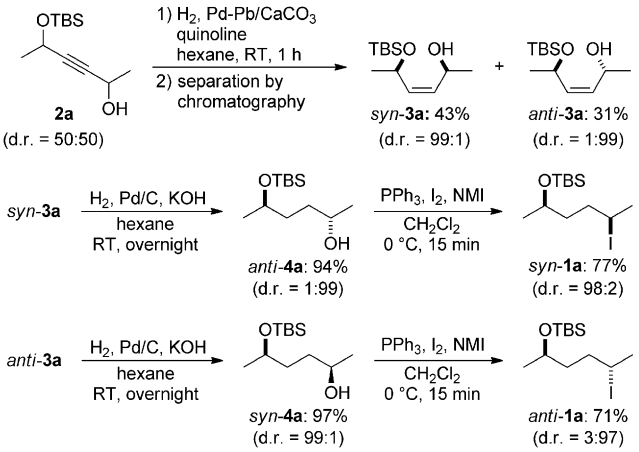
Abstract: *A practical stereoselective iodide–lithium exchange was used in the first general preparation of functionalized stereodefined acyclic secondary nonstabilized lithium reagents from the corresponding secondary alkyl iodides. These lithium reagents react with various electrophiles including carbon electrophiles with high retention of configuration. Kinetic data on the configurational stability of these acyclic alkyllithium reagents are given. This methodology offers a new entry to chiral synthons for the stereoselective synthesis of open-chain molecules.*

Due to their high reactivity, organolithium compounds are important reagents in organic synthesis.[1] In particular, the stereoselective generation of stabilized alkyllithium compounds,[2,3] such as α-heteroatom-substituted alkyl,[4] benzylic,[5,6] and allylic organolithium reagents,[3,6] has been studied extensively as well as their subsequent reactions with electrophiles. However, the preparation of nonstabilized alkyllithium compounds, especially acyclic secondary alkyllithium compounds, and their stereoselective quenching reactions still remain a major synthetic challenge.[7]

Recently, we have shown that secondary cyclohexyllithium reagents can be generated stereoselectively by using an I/Li exchange reaction and subsequent trapping with various electrophiles proceeds in most cases with retention of configuration.[8a] Furthermore, these organolithium compounds have recently gained importance due to their direct use in Pd-catalyzed cross-coupling reactions.[9] Herein, we wish to report the first general preparation of stereodefined acyclic nonstabilized secondary alkyllithium reagents and their quenching reactions with a range of electrophiles including carbon electrophiles.

First, we prepared *syn* and *anti* diastereomers of various acyclic secondary iodides of type **1** using a straightforward synthesis, which is detailed in the case of iodides *syn*-**1a** and *anti*-**1a** (Scheme 1).[10] Thus, a 1:1 mixture of the easily prepared alkynyl alcohols[11] *syn*-**2a** and *anti*-**2a** was partially hydrogenated (Lindlar hydrogenation: H_2, lead-poisoned Pd on $CaCO_3$, quinoline, hexane, RT, 1 h),[12,13] leading to the two chromatographically separable diastereomeric (*Z*)-allylic



Scheme 1. Stereoselective preparation of *syn* and *anti* acyclic secondary alkyl iodides **1a** (d.r. = *syn*/*anti* ratio).

alcohols *syn*-**3a** (43%; d.r. = 99:1) and *anti*-**3a** (31%; d.r. = 1:99). Sequential hydrogenation (H_2, Pd on C, KOH, hexane, RT, overnight)[13] of pure *syn*-**3a** and pure *anti*-**3a** provided the corresponding alcohols, *anti*-**4a** (94%; d.r. = 1:99) and *syn*-**4a** (97%; d.r. = 99:1), respectively, with retention of configuration.[14] Subsequent S_N2 iodination of *syn*-**4a** and *anti*-**4a** (PPh_3, I_2, NMI (*N*-methylimidazole), CH_2Cl_2, 0 °C, 15 min)[15] provided the expected iodides *syn*-**1a** (77%; d.r. = 98:2) and *anti*-**1a** (71%; d.r. = 3:97). The *syn* or *anti* configuration of alcohol **4a** was determined by comparing the ^1H and ^{13}C NMR spectra of the two diastereomers of **4a** with those of *syn*-**4a** obtained from commercially available *syn*-2,5-hexanediol.[10] This allowed us to assign the stereochemistry of *syn*-**1a** and *anti*-**1a** unambiguously.

The alkyl iodide *syn*-**1a** was subjected to an I/Li exchange. Thus, adding *syn*-**1a** dropwise within 10 min to a solution of *t*BuLi in hexane/ether (3:2) at −100 °C (inverse addition) led to the lithium reagent *syn*-**5a**, which was subsequently quenched with Me_2S_2 to afford the thioether *syn*-**6a** in 74% yield with almost complete retention of configuration (d.r. = 96:4; Scheme 2). Similarly, the lithium reagent *anti*-**5a** was prepared from iodide *anti*-**1a**, and was trapped with Me_2S_2 to afford the *anti* thioether *anti*-**6a** in 75% yield with excellent diastereoselectivity (d.r. = 6:94). Treatment of iodide *syn*-**1a**

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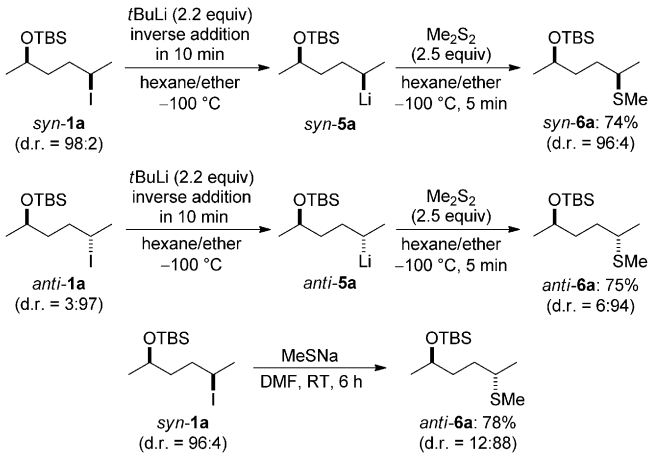


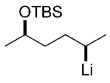
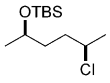
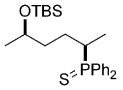
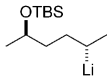
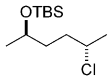
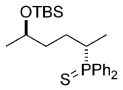
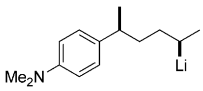
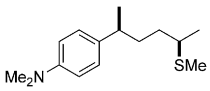
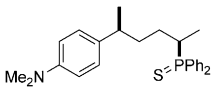
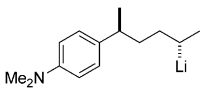
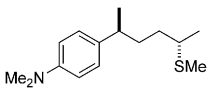
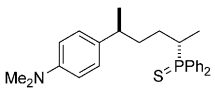
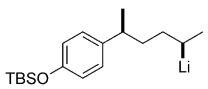
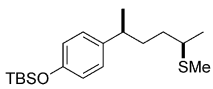
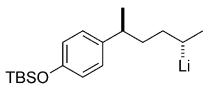
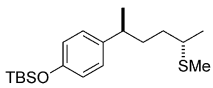
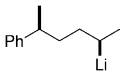
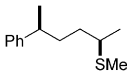
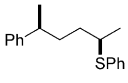
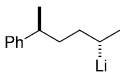
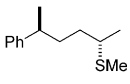
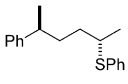
Scheme 2. Stereoselective preparation of *syn* and *anti* acyclic secondary alkyl iodides **1a** (d.r. = *syn*/*anti* ratio).

with sodium methanethiolate led to thioether *anti*-**6a** in 78% yield (d.r. = 12:88) by an S_N2 reaction, which confirmed the overall retention of configuration in the I/Li exchange reaction and subsequent quenching reaction with Me_2S_2 (Scheme 2).

By using these optimized conditions, we were able to stereospecifically access various the new nonstabilized acyclic secondary alkyllithium compounds *syn*- and *anti*-**5a–d** from the corresponding acyclic *syn* and *anti* alkyl iodides **1a–d**[10] through an I/Li exchange and we studied their reactivity with a range of electrophiles (Table 1). Thus, the reactions of *syn*-**5a** with benzenesulfonyl chloride and chlorodiphenylphosphine gave the expected alkyl chloride *syn*-**7** and alkyl diphenylphosphine sulfide *syn*-**8**[16] in 61–81% yield with almost complete retention of configuration (d.r. = 96:4; Table 1, entries 1 and 2), while reactions of *anti*-**5a** with the same electrophiles afforded *anti*-**7** and *anti*-**8**[16] in similar yields (58–82%) with again excellent diastereoselectivities (d.r. = 7:93 and 5:95 respectively; Table 1, entries 3 and 4).

Various *syn* and *anti* aryl-substituted secondary iodides **1b–d** (**1b**: Ar = *p*-$Me_2NC_6H_4$, **1c**: Ar = *p*-$TBSOC_6H_4$, **1d**: Ar = Ph) were also prepared in excellent diastereomeric purity (up to d.r. = 98:2)[10] and subjected to the I/Li exchange reaction (Table 1, entries 5–14). These substituents (*p*-Me_2N;

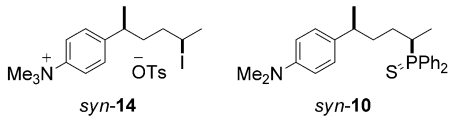
Table 1: Diastereoselective quenching reactions of *syn* and *anti* acyclic secondary alkyllithium reagents **5a–d** with electrophiles.

Entry	Li reagent	E^+	Product	Yield[a] d.r.[b]
1	 *syn*-**5a** (98:2)	$PhSO_2Cl$	 *syn*-**7**	61 96:4
2	*syn*-**5a** (98:2)	Ph_2PCl S_8[16]	 *syn*-**8**	81 96:4
3	 *anti*-**5a** (3:97)	$PhSO_2Cl$	 *anti*-**7**	58 7:93
4	*anti*-**5a** (3:97)	Ph_2PCl S_8[16]	 *anti*-**8**	82 5:95
5	 *syn*-**5b** (96:4)	Me_2S_2	 *syn*-**9**	65 94:6
6	*syn*-**5b** (96:4)	Ph_2PCl S_8[16]	 *syn*-**10**	76 94:6
7	 *anti*-**5b** (8:92)	Me_2S_2	 *anti*-**9**	70 9:91
8	*anti*-**5b** (8:92)	Ph_2PCl S_8[16]	 *anti*-**10**	74 9:91
9	 *syn*-**5c** (98:2)	Me_2S_2	 *syn*-**11**	75 95:5
10	 *anti*-**5c** (2:98)	Me_2S_2	 *anti*-**11**	73 6:94
11	 *syn*-**5d** (98:2)	Me_2S_2	 *syn*-**12**	73 96:4
12	*syn*-**5d** (98:2)	Ph_2S_2	 *syn*-**13**	78 96:4
13	 *anti*-**5d** (8:92)	Me_2S_2	 *anti*-**12**	73 9:91
14	*anti*-**5d** (8:92)	Ph_2S_2	 *anti*-**13**	77 8:92

[a] Yield of isolated product in %. [b] d.r. (*syn*/*anti* ratio) determined by ^{13}C NMR spectroscopy.

entries 5–8 and *p*-TBSO; entries 9 and 10) are well tolerated and the I/Li exchange proceeds with high stereoselectivity in all cases. After quenching with Me_2S_2, Ph_2PCl,[16] or Ph_2S_2, the expected products *syn*- or *anti*-**9**–**13** were obtained in 65–77% yield with retention of configuration (up to d.r. = 96:4 and 6:94, respectively; Table 1, entries 5–14).

In order to determine the relative stereochemistry of the secondary alkyl iodides **1b–d** and the products **9**–**13**, two X-ray crystallographic analyses were performed.[17] Thus, the quaternary ammonium tosylate *syn*-**14**[17] was prepared by the reaction of *syn*-**1b** with methyl tosylate in acetone (Figure 1). After recrystallization from chloroform, the relative stereochemistry of this salt was unambiguously determined by X-ray crystallographic analysis to be *syn*. Moreover, the *syn* stereochemistry of the phosphorus compound *syn*-**10**[17] could also be confirmed by X-ray crystallographic analysis, thus verifying the overall retention of configuration for the I/Li exchange and quenching sequence.[10]



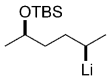
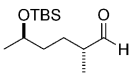
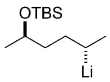
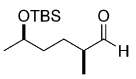
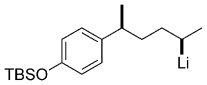
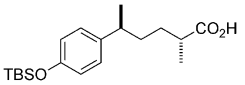
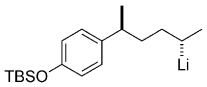
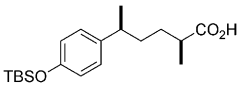
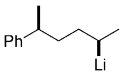
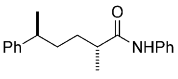
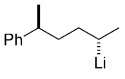
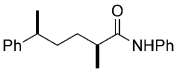
syn-**14** *syn*-**10**

Figure 1. Structures of *syn*-**14** and *syn*-**10** confirmed by X-ray crystallographic analyses.

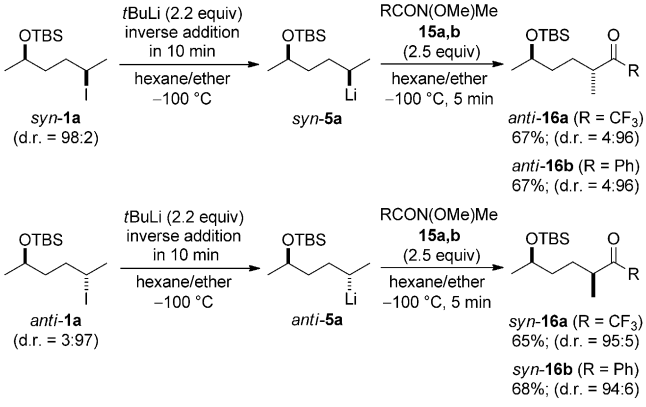
The stereoselective formation of carbon–carbon bonds using these acyclic secondary alkyllithium reagents was also investigated (Scheme 3 and Table 2). Remarkably, the reaction of alkyllithium compounds *syn*-**5a** and *anti*-**5a** with Weinreb amides[18] **15a**,**b** (**15a**: R = CF_3, **15b**: R = Ph) led to the expected α-chiral trifluoromethyl ketone[19] **16a** and phenyl ketone **16b** in 65–68% yield with almost complete retention of configuration[4w] (up to d.r. = 4:96 and 95:5; Scheme 3). Diastereoselective formylation,[4d] carboxylation,[4b,v,7e] and amidation[4l,8a] were also readily achieved by treating the lithium reagents **5a**, **5c**, and **5d** with DMF, CO_2, and PhNCO, respectively (Table 2).

We have shown recently that the *cis*-4-*tert*-butylcyclohexyllithium reagent *cis*-(*ax*)-**20** epimerizes very rapidly at −100 °C (Scheme 4a).[8a,20] In this context we examined the epimerization kinetics of the lithium compounds *syn*-**5a** and *anti*-**5a** under standard conditions at −100 °C (●, ◆) and −90 °C (▲, ■) as shown (Scheme 4b) by retentive quenching with Me_2S_2 after different times. The plot of the epimerization percentage for *syn*-**5a** versus time resulted in monoexponential decays, showing that the epimerizations proceed by first-order reversible reactions. The rate constants for the epimerization of *syn*-**5a** and *anti*-**5a** at −90 °C (■) were calculated from Equation (1).[21] The slopes of the resulting straight lines provided the value of $(k_1 + k_{-1})$ and the individual rate constants k_1 and k_{-1} were readily determined from the equilibrium concentrations at $t = 7$ h, when the equilibrium *syn*/*anti* = 60:40 was reached ($k_{-1}/k_1 = 1.5$). We found that at −90 °C the rate constants k_1 and k_{-1} for the epimerization of *syn*-**5a** and *anti*-**5a** were equal to $1.28 \times 10^{-4}\ s^{-1}$ and $1.92 \times 10^{-4}\ s^{-1}$, respectively. The Gibbs free energy ΔG° (0.62 kJ mol^{-1} at −90 °C) indicated that *syn*-**5a** and *anti*-**5a** have almost the same configurational stability.[8a] Interestingly, epimerization of *syn*-**5a** at −100 °C was much slower than that of *cis*-(*ax*)-**20** (1,3-diaxial interactions may destabilize this lithium reagent),[8a] explaining the higher configurational stability of these acyclic secondary alkyllithium reagents. In the case of *syn*-**5a**, even after 1 h at −100 °C, the *syn*/*anti* ratio was still remaining high (92:8), confirming the experimental observation that the iodides **1a–d** can be

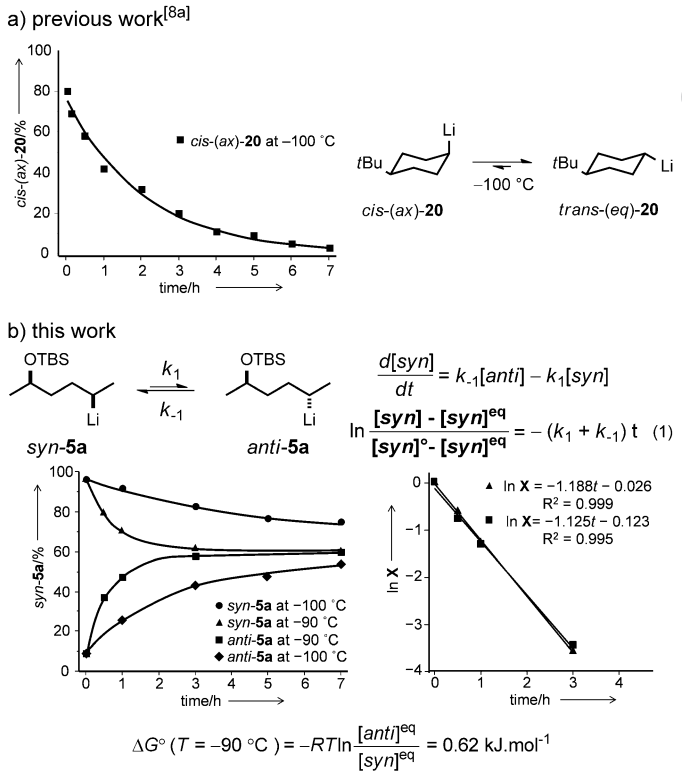
Table 2: Diastereoselective formylation, carboxylation, and amidation of *syn* and *anti* acyclic secondary alkyllithium reagents **5a**, **5c**, and **5d**.

Entry	Li reagent	E^+	Product	Yield[a] d.r.[b]
1	 *syn*-**5a** (98:2)	DMF	 *anti*-**17**	80 8:92
2	 *anti*-**5a** (3:97)	DMF	 *syn*-**17**	70 91:9
3	 *syn*-**5c** (98:2)	CO_2	 *anti*-**18**	79 6:94
4	 *anti*-**5c** (2:98)	CO_2	 *syn*-**18**	77 95:5
5	 *syn*-**5d** (98:2)	PhNCO	 *anti*-**19**	80 4:96
6	 *anti*-**5d** (8:92)	PhNCO	 *syn*-**19**	80 92:8

[a] Yield of isolated product in %. [b] d.r. (*syn*/*anti* ratio) determined by ^{13}C NMR spectroscopy.



Scheme 3. Stereoselective preparation of *syn* and *anti* acyclic secondary alkyl iodides **1a** (d.r. = *syn*/*anti* ratio).



Scheme 4. Kinetic investigation of the equilibration between *syn*-**5a** and *anti*-**5a** at −100 °C and −90 °C and determination of the Gibbs free energy $\Delta G°$ of this equilibrium.

added dropwise within 10 min to the solution of *t*BuLi without any significant loss of diastereoselectivity.

In summary, we have developed the first practical preparation of stereodefined acyclic secondary alkyllithium reagents from their corresponding secondary alkyl iodides. Some functionalities were tolerated during this I/Li exchange reaction, and the corresponding lithium derivatives were quenched with a range of electrophiles. In particular, several classes of carbon electrophiles were successfully used, thus allowing access to various carbonyl compounds, carboxylic acids, and amides bearing a stereocenter in the α-position with excellent diastereoselectivities and overall retention of configuration. This methodology opens new possibilities for constructing chiral open-chain molecules. Thus, new chiral synthons[22] such as *syn*-**21** and *anti*-**21** (Figure 2) are now available to form new carbon–carbon bonds with high stereoselectivities since the required enantiomerically pure starting secondary alkyl iodides can be prepared from the corresponding chiral alcohols.[23] Further extension of this methodology to make available other chiral synthons and their quenching reactions with other electrophiles are currently being studied.

Figure 2. Chiral synthons *syn*-**21** and *anti*-**21** obtained from the stereoselective I/Li exchange. (a = acceptor, d = donor)[22]

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