Alkyllithium Reagents

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Stereoselective Synthesis and Reactions of Secondary Alkyllithium Reagents Functionalized at the 3-Position**

*Kohei Moriya, Dorian Didier, Meike Simon, Jeffrey M. Hammann, Guillaume Berionni, Konstantin Karaghiosoff, Hendrik Zipse, Herbert Mayr, and Paul Knochel**

Dedicated to Professor Dieter Seebach on the occasion of his 77th birthday

Abstract: *Secondary alkyllithium reagents bearing an OTBS group (TBS = tert-butyldimethylsilyl) at the 3-position can be prepared stereoconvergently through an I/Li exchange from a diastereomeric mixture of the corresponding secondary alkyl iodides. These lithium reagents react with a range of electrophiles, including carbon electrophiles, with retention of configuration to yield various 1,3-difunctionalized derivatives with good diastereoselectivities. Kinetic studies show that the 3-siloxy group strongly accelerates the epimerization at the lithium-substituted carbon atom. This method offers a new way to construct chiral open-chain molecules with excellent stereoselectivity.*

Organolithium reagents occupy a central position in organic synthesis.[1] Their exceptionally high reactivity combined with the availability of a range of practical preparation methods has led to an increase in the use of these organometallic compounds in organic synthesis.[2] However, despite several reports,[3] the stereoselective preparation of non-heteroatom-stabilized secondary alkyllithium reagents has been a difficult task.[4,5] Recently, we have shown that an I/Li exchange can be used for stereoselectively preparing various substituted cyclohexyllithium reagents[6] as well as acyclic secondary alkyllithium reagents bearing a functional group (FG = OTBS, Ph; TBS = *tert*-butyldimethylsilyl) at a remote position.[7] This study demonstrated the high synthetic potential of functionalized secondary alkyllithium reagents of type **1** and led us to investigate the stereoselective synthesis of 3-functionalized secondary alkyllithium reagents of type **2** (Figure 1).

We anticipated that the close proximity of the functional group (FG = OTBS, Ph) to the carbon–lithium bond might influence the preparation of these secondary lithium reagents. Herein, we report the stereoselective synthesis of various secondary alkyllithium reagents of type **2**. We demonstrate the strong effect of the OTBS group on the stereoconvergence that occurs during I/Li exchange and show that these lithium reagents react with retention of configuration with various electrophiles, including carbon electrophiles.

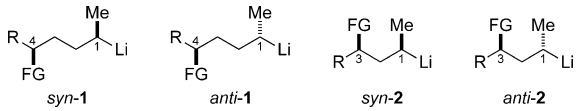
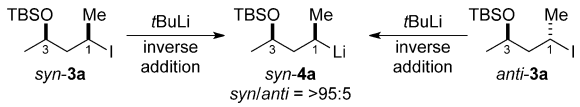


Figure 1. 1,4- and 1,3-functionalized secondary alkyllithium reagents.

First, we prepared various secondary iodides bearing a protected hydroxy group at the 3-position. After extensive optimization,[8] we found that compared with other protecting groups, a OTBS moiety was most suitable. Thus, the addition (inverse addition)[9] of *syn*-alkyl iodide *syn*-**3a** to *t*BuLi (2.5 equiv, −100 °C to −50 °C, in a 1:3 mixture of diethyl ether/*n*-hexane) led to *syn*-lithium species *syn*-**4a** with a diastereoselectivity of approximately 95:5, which was determined after quenching with Bu_2S_2 (Scheme 1).[8] Interestingly, *anti*-iodide *anti*-**3a** also yielded the *syn*-lithium species *syn*-**4a** with the same diastereoselectivity with this procedure. This stereoconvergence implies that the configuration at the iodine-substituted carbon atom is inconsequential. Therefore, we used a mixture of *syn*- and *anti*-**3a** in all further experiments. Under these conditions, quenching of *syn*-**4a** with various electrophiles led to a range of products of type **5** (Table 1). As mentioned above, the generation of alkyllithium species *syn*-**4a** from a 1:1 *syn*/*anti* mixture of **3a** and trapping with Bu_2S_2 led to thioether **5a** in 75% yield and d.r. = 93:7 (entry 1). Remarkably, a range of carbon electrophiles also reacted with the lithium reagent *syn*-**4a**. Quenching of *syn*-**4a** with DMF,[7] an acid chloride,[10] ethyl chloroformate, or PhNCO[7] led to the expected carbonyl derivatives **5b–e** in 67–74% yield and *syn*/*anti* ratios of up to 97:3 (entries 2–5). Moreover, 3-pentanone reacted with *syn*-**4a** to provide tertiary alcohol **5f** in 55% yield and d.r. = 97:3 (entry 6).[11] Trapping of *syn*-**4a** with methyl pinacolyl borate led to boronic acid pinacol ester **5g** in 73% yield (d.r. = 97:3; entry 7).[12] Alkylation of *syn*-**4a** with ethoxymethyl chloride



Scheme 1. Diastereoconvergent preparation of secondary alkyllithium reagent *syn*-**4a** from **3a**. (inverse addition: **3a** was added to *t*BuLi).

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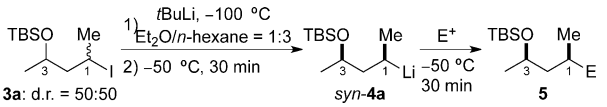
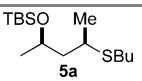
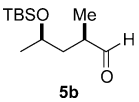
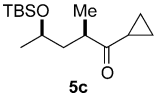
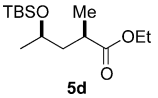
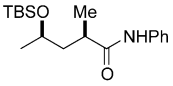
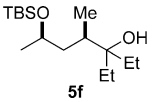
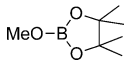
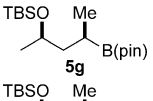
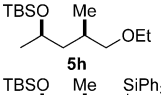
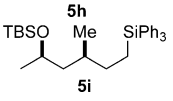
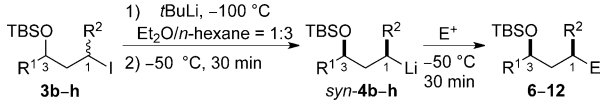
Table 1: Stereoconvergent I/Li exchange on the 3-silyloxy-substituted secondary alkyl iodides **3a** and diastereoselective quenching reactions.

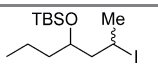
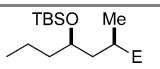
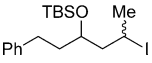
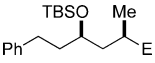
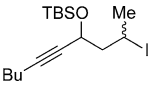
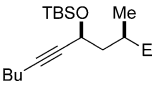
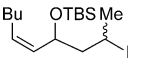
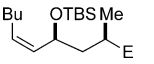
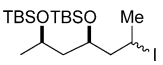
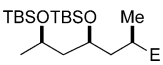
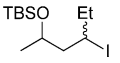
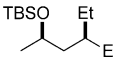
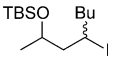
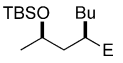


Entry	E^+ (Electrophile)	Product	Yield[a] [%]	d.r.[b]
1	Bu_2S_2	 **5a**	75	93:7
2	DMF	 **5b**	74	92:8
3		 **5c**	67	96:4
4		 **5d**	70[c]	97:3
5	Ph−N=C=O	 **5e**	69[d]	96:4
6		 **5f**	55	99:1
7		 **5g**	73	97:3
8		 **5h**	60[c]	99:1
9		 **5i**	65[c]	99:1

[a] Yield of isolated product. [b] Diastereomeric ratio (*syn*/*anti*) determined by GC and NMR analysis. [c] Gram-scale reaction. [d] Yield after deprotection with TBAF·3 H_2O. Bpin = pinacolyl borate, TBAF = tetrabutylammonium fluoride.

Table 2: Stereoconvergent I/Li exchange on the 3-silyloxy-substituted secondary alkyl iodides **3b–h** and diastereoselective quenching reactions.



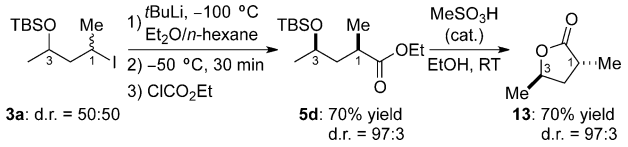
Entry	Substrate	Product		Yield [%][a]	d.r.[b]
					
1	**3b**: d.r. = 66:34	**6a**	E = SBu	58	94:6
2		**6b**	E = CHO	61	91:9
3		**6c**	E = B(pin)	65	97:3
					
4	**3c**: d.r. = 62:38	**7a**	E = SBu	62	93:7
5		**7b**	E = CO_2Et	64	93:7
6		**7c**	E = B(pin)	69	97:3
					
7	**3d**: d.r. = 50:50	**8a**	E = SBu	58	90:10
8		**8b**	E = CO_2Et	57	98:2
					
9	**3e**: d.r. = 50:50	**9a**	E = SBu	67	95:5
10		**9b**	E = CO_2Et	77	97:3
11		**9c**	E = B(pin)	60	99:1
					
12	**3f**: d.r. = 63:37	**10a**	E = SBu	69	91:9
13		**10b**	E = CO_2Et	71	96:4
					
14	**3g**: d.r. = 50:50	**11a**	E = SBu	65	86:14
					
15	**3h**: d.r. = 50:50	**12a**	E = SBu	63	86:14

[a] Yield of isolated product. [b] Diastereomeric ratios (*syn*/*anti*) determined by GC and NMR analysis.

furnished ether **5h** in 60% yield (d.r. = 99:1; entry 8).[13] Finally, *syn*-**4a** underwent a carbolithiation reaction with triphenylvinylsilane to form silane **5i** in 65% yield and d.r. = 99:1 (entry 9).[14] Furthermore, the scale-up of our procedure to gram scale was straightforward (entries 4, 8, and 9).

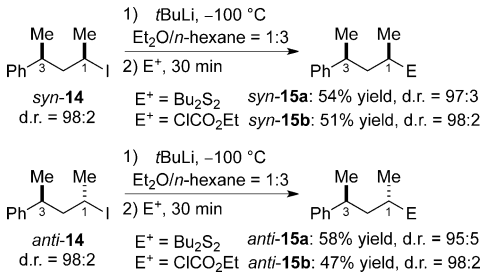
To evaluate the substrate scope, we prepared various 3-siloxy-substituted secondary alkyl iodides (Table 2). First, we replaced the 3-methyl substituent in **3a** by a propyl (**3b**) or a phenethyl group (**3c**). In both cases, the same high stereoconvergence was observed, and quenching reactions with electrophiles, such as Bu_2S_2, DMF, MeO−B(pin), or $ClCO_2Et$, gave **6a–c** and **7a–c** in 58–69% yield and d.r. ≥ 91:9 (Table 2, entries 1–6). The 3-methyl group was also replaced by an alkynyl (**3d**) or alkenyl group (**3e**) to obtain the expected *syn* products **8a–b** and **9a–c** in 57–77% yield and diastereoselectivities of up to 99:1 (entries 7–11). Finally, we also prepared secondary alkyl iodide **3f**, which bears two OTBS groups and may be relevant for the construction of natural-product carbon chains with 1,3-functionality.[15] The corresponding lithium reagent reacted with Bu_2S_2 or $ClCO_2Et$ in 69–71% yield and d.r. ≥ 91:9 (entries 12 and 13). In all of these examples (Tables 1 and 2), high diastereoselectivities were observed, showing that the nature of the substituents strongly favors lithium reagent *syn*-**4**. For the last two substrates, replacement of the 1-methyl substituent of **3a** by an ethyl (**3g**) or butyl group (**3h**) led to lower diastereoselectivities (86:14, compared to 93:7 for **5a**). We have also applied this method for the stereoselective synthesis of disubstituted butyrolactone **13**.[16] Thus, treatment of **5d** with $MeSO_3H$ (10 mol%) produced *trans*-lactone **13** in 70% yield (d.r. = 97:3; Scheme 2).

Having established that 3-siloxy-substituted alkyl iodides **3a–h** underwent a stereoconvergent reaction yielding the corresponding lithium reagents, we also examined the lith-



Scheme 2. Stereoselective synthesis of *trans*-2,4-dimethylbutyrolactone (**13**).

iation of 3-phenyl-substituted iodide **14**. Therefore, both *syn*- and *anti*-**14** were treated with *t*BuLi at −100 °C in diethyl ether/*n*-hexane (1:3). At this low temperature, epimerization at the lithium-substituted carbon atom was hardly observed, and quenching with either Bu_2S_2 or $ClCO_2Et$ gave *syn*- and *anti*-**15a/b** in 47–58 % yield with retention of configuration (Scheme 3). This result contrasts the behavior of 3-siloxy-substituted alkyllithium reagents.



Scheme 3. Stereoselective Li/I exchange on 3-phenyl-substituted secondary alkyl iodides (*anti*- and *syn*-**14**) and stereoselective quenching reactions.

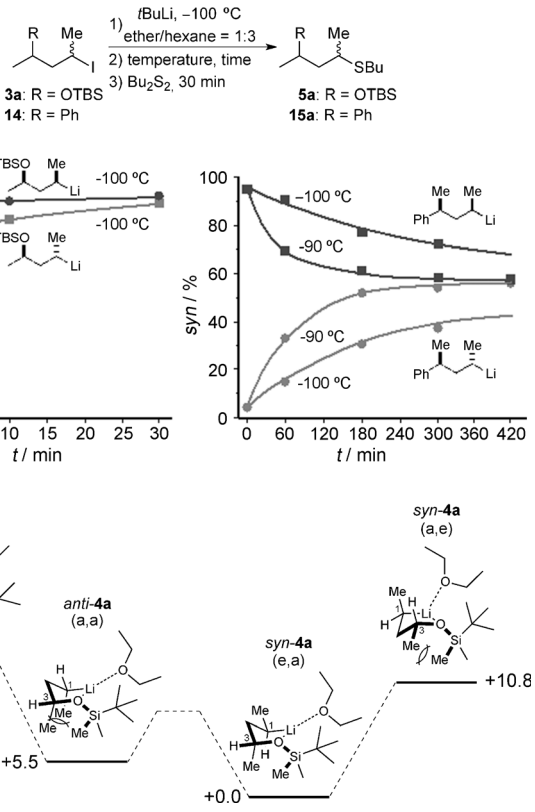


Figure 2. Kinetic studies of the epimerization of secondary alkyllithium reagents generated from *syn*- and *anti*-**3a** and **14**, and relative free energies at −100 °C [ΔG_{173}, in kJ mol^{-1}] for *syn*- and *anti*-**4a** (complexed to one diethyl ether molecule).

To explain these different behaviors, we studied the epimerization kinetics of the alkyllithium derivatives of the *syn*- and *anti*-isomers of **3a** and **14** (Figure 2).[3e,17,18] We found that the epimerization rates of the 3-siloxy-substituted alkyllithium reagents are much greater than those of the 3-phenyl-substituted alkyllithium reagents.[19] As shown in the quantum chemically calculated[20] free energy diagram in Figure 2, the alkyllithium reagents *syn*- and *anti*-**4a** adopt a five-membered ring structure owing to chelation between the oxygen and lithium atoms. The steric interaction between the silyl group and the 3-methyl group is avoided when the latter is located in an axial position (*syn*-**4a** (e,a) and *anti*-**4a** (a,a)). As *anti*-**4a** (a,a) is destabilized by 5.5 kJ mol^{-1} through steric interactions between the two axial methyl groups, *syn*-**4a** (e,a) is the most stable structure, and *anti*-**4a** epimerizes to *syn*-**4a**, leading to the observed stereoconvergence.[21] Calculations[8] show that the *syn*- and *anti*-organolithium compounds that are derived from the phenyl-substituted derivatives *syn*- and *anti*-**14a** are of similar energies because there are no interactions between the phenyl ring and the lithium atom (Figure 2).

In summary, we have shown that 3-*tert*-butyldimethylsilyloxy-substituted alkyllithium compounds can be generated in a stereoconvergent way by I/Li exchange and trapped by electrophiles with retention of configuration. Such a stereoconvergent process was not observed for 3-phenyl-substituted alkyllithium reagents, as the two diastereomers were generated stereoselectively from the respective diastereomeric alkyl iodide precursors, indicating that the OTBS group is essential for the stereoconvergence. Kinetic studies showed that epimerization is much faster for the 3-OTBS-substituted alkyllithium reagents than for the corresponding 3-phenyl-substituted analogues (Figure 2). This observation can be explained by the O–Li coordination, which increases the ionic character of the C–Li bond and thus facilitates epimerization at the 1-position. Furthermore, the 1,3-relationship between the C–Li bond and the oxygen functional group may be useful for the stereoselective construction of natural products. Such applications are currently studied in our laboratories.

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Keywords: carbanions · diastereoselectivity · kinetics · lithiation · nucleophilic substitution

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