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Preparation of Stereodefined Secondary Alkyllithium Compounds

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Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

Abstract: We have developed a practical stereoretentive iodine/lithium-exchange process that allows the stereodefined preparation of *cis*- and *trans*-cycloalkyllithium compounds from their corresponding stereodefined iodides. Quenching with electrophiles offers stereospecific access to both *cis*- (up to 96% *cis*) and *trans*-cycloalkyl derivatives (up to 99% *trans*). A detailed study of the thermodynamic stabilities, stereochemical behavior, and reactivities of axially and equatorially substituted cyclohexyllithium reagents is reported. Ab initio calculations demonstrate that the formation of oligomeric cyclohexyllithium structures is pivotal for explaining the observed stereochemical preference.

Keywords: diastereoselectivity · lithiation · solvent effects · substituent effects · synthetic methods

Introduction

Owing to their superior reactivity and ready availability, organolithium compounds have become frequently used key intermediates in the synthesis of natural products, pharmaceuticals, agrochemicals, and unnatural materials.[1] As such, the stereoselective preparation of α-chiral alkyllithiums has been one of the most active fields of research in organometallic chemistry.[2]

Although the stereochemical behavior of stabilized alkyllithiums,[2,3,4] such as α-heteroatom-substituted alkyl-,[5] benzylic,[6,7] and allylic organolithium reagents,[3,7] have been extensively studied, owing to their more straightforward preparation, the stereoselective synthesis of non-stabilized secondary alkyllithiums has remained a major synthetic challenge.[8] Pioneering work by Reich et al. showed that a Te/Li exchange can be used to stereospecifically access such secondary alkyllithium reagents.[9a] Moreover, lithium insertion into the carbon–chlorine bond of 4-*tert*-butylcyclohexyl chloride and menthyl chloride has been performed and gives the corresponding *trans*-lithium derivatives.[9b,c] The more practical I/Li exchange has been well-documented for primary alkyl and unsaturated organic bromides and iodides.[10] However, much less success has been encountered with secondary alkyl halides, although this process was applied to a configurationally rigid polycyclic system by Ishihara and co-workers, who afforded the equatorial lithium species in excellent yield with retention of configuration.[11] Subsequent trapping with a chlorine or bromine electrophile produces the corresponding halo derivatives, again with retention of configuration. In general, I/Li exchange could not be efficiently used for the preparation of secondary cyclohexyllithiums, owing to excessive elimination and protonation side-reactions. Herein, we report a method for the successful suppression of these side-reactions, thus opening, for the first time, a direct practical access to stereodefined non-stabilized substituted-cyclohexyllithium reagents from the readily available cyclohexyl iodides.[12] The stereochemical course of these reactions with typical electrophiles was determined and their thermodynamic stabilities were investigated. Our experimental observations were rationalized with the support of theoretical calculations.

Results and Discussion

Initial experiments showed that the addition of *t*BuLi to a solution of *cis*-4-*tert*-butylcyclohexyl iodide, ***cis*-(ax)-1**, in *n*-hexane/Et_2O (3:2)[10e] at −100 °C mainly gave the protonation and elimination products (**2** and **3**, respectively, Scheme 1). This result was due to the very similar reactivity of *t*BuLi and the newly formed secondary *cis*-cyclohexyllithium, ***cis*-(ax)-4**. Moreover, the mode of addition implies the presence of excess amounts of ***cis*-(ax)-1** relative to the organolithium species, thus favoring elimination side-reactions. These conditions result in a low yield of ***cis*-(ax)-4** (<7%, as determined by quenching experiments, see below). However, inversion of the order of addition[10g,i] led to an efficient suppression of unwanted protonation and elimination pathways and the desired secondary organolithium **4** was obtained in 70–90% yield.[13]

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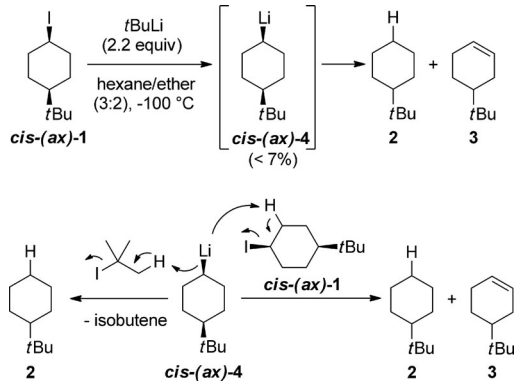
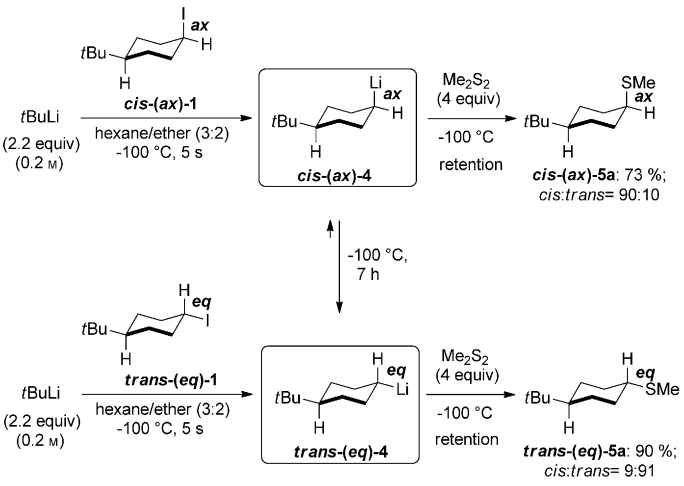


Scheme 1. Formation of protolysis and elimination side-products during I/Li exchange on ***cis*-(ax)-1**.

By using these optimized conditions, we were able to stereospecifically access various new non-stabilized cyclohexyllithium compounds and, consequently, monitor their stereochemical behavior. Thus, we prepared stereodefined *cis*- and *trans*-4-*tert*-butylcyclohexyl iodides ***cis*-(ax)-1**[14] (*cis*/*trans*, 98:2) and ***trans*-(eq)-1** (*cis*/*trans*, 10:90) from their respective alcohols[12] and subjected them to our I/Li-exchange conditions (see above). The addition of stereodefined ***trans*-(eq)-1** to a solution of *t*BuLi instantaneously produced *trans*-cyclohexyllithium ***trans*-(eq)-4**; immediate quenching (after 5 s) with Me_2S_2 led to the expected *trans*-thioether, ***trans*-(eq)-5a**, with retention of configuration (*cis*/*trans*, 9:91) in 90% yield (Scheme 2). Notably, ***trans*-(eq)-4**, in which the Li atom occupied an equatorial position, was stable at −100 °C (probed over 7 h).

Subjecting ***cis*-(ax)-1** to the same conditions produced the axially substituted lithium reagent ***cis*-(ax)-4**. Quenching with Me_2S_2 mainly gave the corresponding *cis*-thioether, ***cis*-(ax)-5a** (*cis*/*trans*, 90:10), in 73% yield. Lithium species ***cis*-(ax)-4**, in which the Li atom occupied an axial position, displayed much lower thermodynamic stability and fully equilibrated into the stable all-equatorially substituted ***trans*-(eq)-4** within 7 h at −100 °C (*cis*/*trans*, <3:97; also see the detailed kinetic and theoretical studies on the relative thermodynamic stabilities below). The lower stability of ***cis*-(ax)-4** compared to its diastereomer, ***trans*-(eq)-4**, is also likely to account for this slightly lower yield. Next, the reactivity of ***trans*-(eq)-4** and ***cis*-(ax)-4** towards a variety of electrophiles was examined (Table 1). Whilst the reactions of ***trans*-(eq)-4**



Scheme 2. Retention of configuration during I/Li exchange on equatorially (***trans*-(eq)-1**) and axially substituted (***cis*-(ax)-1**) diastereomeric cyclohexyl iodides.

Table 1. Reactivity of ***trans*-4** and ***cis*-4** with different electrophiles.

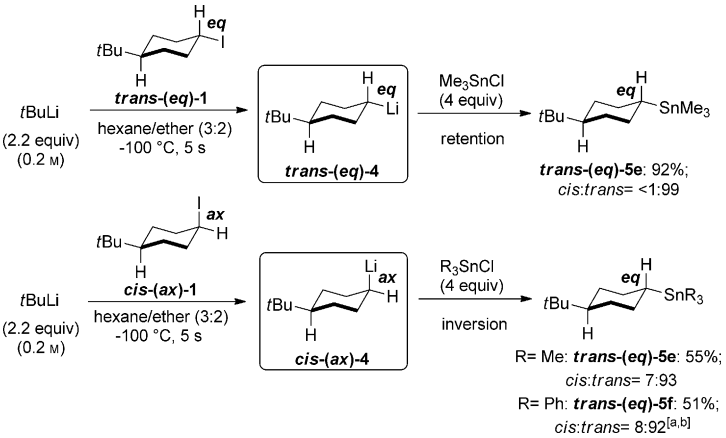
	Li reagent	E^+	Product	Yield [%][a]	d.r.[b]
1	***trans*-(eq)-4**	Bu_2S_2	***trans*-(eq)-5b**	85	<1:99
2	***trans*-(eq)-4**	PhNCO	***trans*-(eq)-5c**	87	<1:99
3	***trans*-(eq)-4**	F_3CCO_2D	***trans*-(eq)-5d**	85[c]	4:96[d]
4	***cis*-(ax)-4**	Bu_2S_2	***cis*-(ax)-5b**	59	90:10
5	***cis*-(ax)-4**	PhNCO	***cis*-(ax)-5c**	60	90:10
6	***cis*-(ax)-4**	F_3CCO_2D	***cis*-(ax)-5d**	75[c]	92:8[d]

[a] Yield of isolated product. [b] *cis*/*trans* (axial/equatorial) ratio, as determined by capillary GC analysis and ^{1}H NMR spectroscopy. [c] Determined by capillary GC analysis. [d] Determined by ^{2}H NMR spectroscopy.

with a range of electrophiles proceeded with retention of the configuration, thereby leading to the expected *trans*-substituted products in 85–87% yield and with excellent stereoselectivities (up to d.r. >99:1; Table 1, entries 1–3), quenching of the thermodynamically less stable ***cis*-(ax)-4** was not as predictable. Trapping of ***cis*-(ax)-4** with Bu_2S_2, [D]TFA (TFA = trifluoroacetic acid), and PhNCO stereospecifically provided the expected *cis* products (***cis*-(ax)-5b–d**; Table 1 entries 4–6). Owing to the lability of cyclic organolithium ***cis*-(ax)-4**, lower yields (59–75%) than in the reactions of ***trans*-(eq)-4** were generally obtained. The instability of ***cis*-(ax)-4** also accounts for the lower stereoselectivities in these retentive quenching reactions.

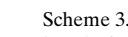
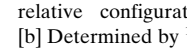
The reaction of cyclohexyllithium ***trans*-(eq)-4** with Me_3SnCl gave the expected *trans*-substituted product, ***trans*-(eq)-5e** (*cis*/*trans*, <1:99), in 92% yield with complete retention of the configuration (Scheme 3).[15] However, quenching of the thermodynamically less stable ***cis*-(ax)-4** with either Me_3SnCl or Ph_3SnCl proceeded preferentially with overall inversion of configuration at the C–Li bond, thus mainly resulting in *trans*-substituted stannanes ***trans*-(eq)-5e,f**.[16]

Replacing the *t*Bu group with coordinating (MeO, ***trans*-(eq)-6a**) or non-coordinating oxygen functionalities (TIPSO, TIPS = triisopropylsilyl, ***trans*-(eq)-6b**) led, after quenching,



Scheme 3. Retention of configuration during the quenching of equatorially substituted ***trans*-(eq)-4** with organotin chlorides and inversion of configuration during the quenching of axially substituted ***cis*-(ax)-4**. [a] The relative configuration was determined by X-ray crystallography.[14] [b] Determined by ^{119}Sn NMR spectroscopy.

Table 2. Scope of the I/Li exchange by using equatorially and axially substituted cyclohexyl iodides that contained coordinating and non-coordinating oxygen functionalities.

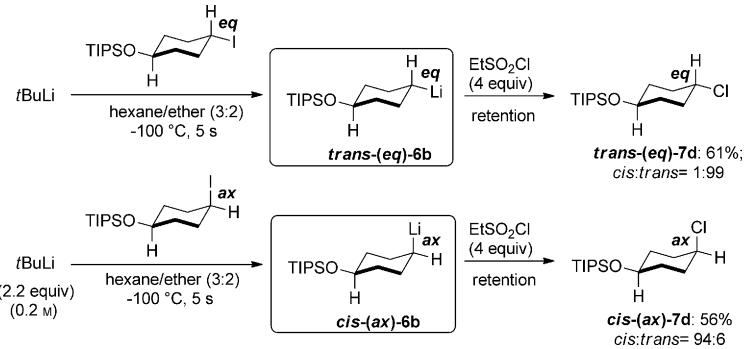
	Li reagent	E^+	Product	Yield [%][a]	d.r.[b]
1	***trans*-(eq)-6a**	Bu_2S_2	***trans*-(eq)-7a**	83	<1:99
2	***trans*-(eq)-6b**	Bu_2S_2	***trans*-(eq)-7b**	90	1:99
3	***trans*-(eq)-6b**	Ph_2PCl, S_8	***trans*-(eq)-7c**	69	2:98
4	***cis*-(ax)-6a**	Bu_2S_2	**7a**	67	52:48
5	 ***cis*-(ax)-6b**	Bu_2S_2	***cis*-(ax)-7b**	79	96:4
6	***cis*-(ax)-6b**	Ph_2PCl, S_8	 ***cis*-(ax)-7c**	51	92:8

[a] Yield of isolated product. [b] axial/equatorial ratio, as determined by capillary GC analysis and ^{1}H NMR spectroscopy.

to the expected *trans*-substituted products with equally high yields and diastereoselectivities (83–90% yield, d.r. > 99:1; Table 2, entries 1 and 2). Trapping of functionalized organolithium reagent ***trans*-(eq)-6b** with Ph_2PCl and subsequent protection with S_8 gave *trans*-substituted thiophosphane ***trans*-(eq)-7c** in 69% overall yield and a d.r. of 98:2 (Table 2, entry 3).

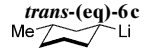
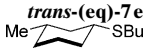
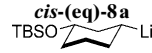
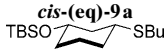
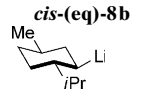
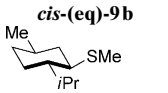
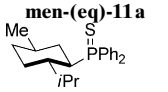
Remarkably, immediate quenching of 4-methoxy-substituted ***cis*-(ax)-6a**, which was generated from the corresponding stereochemically pure iodide, with Bu_2S_2 led to a mixture of thioether **7a** (*cis*/*trans* (ax/eq), 52:48; Table 2, entry 4). We reasoned that this loss of stereoselectivity could be attributed to the coordinative properties of the 4-MeO group. Because the coordinative oxygen atom of Et_2O shows no effect on the stereoselectivity, we surmised that the MeO group may intramolecularly break the unstable axial C–Li bond and facilitate its isomerization into the thermodynamically more stable ***trans*-(eq)-6a**. Indeed, complete isomerization from ***cis*-(ax)-6a** into ***trans*-(eq)-6a** took place within only 2.5 min at −100 °C in a *n*-hexane/Et_2O (3:2) mixture (*cis*/*trans* 2:98; also see the detailed kinetic studies on the configurational behavior below; Scheme 6b), whereas the corresponding 4-*tert*-butyl-substituted axial cyclohexyllithium ***cis*-(ax)-4** required 7 h under the same conditions to isomerize into the stable equatorial cyclohexyllithium compound ***trans*-(eq)-4** (also see Scheme 6a). Interestingly, accelerated isomerization was not observed with an OTIPS substituent and the desired *cis*-configured products, ***cis*-(ax)-7b**,**c**, were obtained, upon quenching, in 51–79% yield with stereoselectivities of up to 96:4 (Table 2, entries 5 and 6). The bulky silyl group prevents the neighboring oxygen atom from coordinating to the Li^+ ion. Interestingly, quenching of ***trans*-(eq)-6b** and ***cis*-(ax)-6b** with $EtSO_2Cl$ stereospecifically provided their respective cyclohexyl chlorides with high diastereoselectvities (Scheme 4).

Next, we varied the substitution pattern on the cyclohexyl iodides, which we subsequently subjected to the exchange conditions. First, we focused on the reactions of equatorially substituted cyclohexyllithiums (Table 3). Thus, 4-methyl-substituted ***trans*-(eq)-6c** was stereospecifically prepared from the corresponding iodide and exclusively provided, upon trapping with Bu_2S_2, *trans*-configured thioether ***trans*-(eq)-7e** in 91% yield (Table 3, entry 1). The *cis*-1,3-disubstituted cyclohexyl iodides smoothly underwent the I/Li-exchange reaction. The resulting equatorially substituted Li reagents, ***cis*-(eq)-8a**,**b**, were trapped with Bu_2S_2, thereby leading to



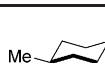
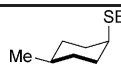
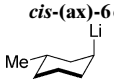
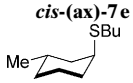
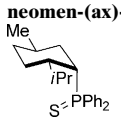
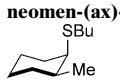
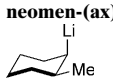
Scheme 4. Stereospecific preparation of cyclohexyl chloride through the quenching of ***trans*-(eq)-6b** and ***cis*-(ax)-6b** with $EtSO_2Cl$.

Table 3. Scope of the I/Li exchange by using equatorially substituted cyclohexyl iodides and quenching of the ensuing Li species with various electrophiles.

	Li reagent	E^+	Product	Yield [%][a]	d.r.[b]
					
1	***trans*-(eq)-6c** 	Bu_2S_2	***trans*-(eq)-7e** 	91	<1:99
2	***cis*-(eq)-8a** 	Bu_2S_2	***cis*-(eq)-9a** 	81	<1:99
3	***cis*-(eq)-8b** 	Bu_2S_2	***cis*-(eq)-9b** 	63	2:98
4	**men-(eq)-10**	Me_2S_2	**men-(eq)-11a** 	54	13:87
5	**men-(eq)-10**	Ph_2PCl, S_8	**men-(eq)-11b**	59	10:90[c]

[a] Yield of isolated product. [b] Axial/equatorial ratio, as determined by capillary GC analysis and ^1H NMR spectroscopy. [c] Determined by ^{31}P NMR spectroscopy.

Table 4. Scope of the I/Li exchange by using equatorially and axially substituted cyclohexyl iodides and quenching of the ensuing Li species with various electrophiles.

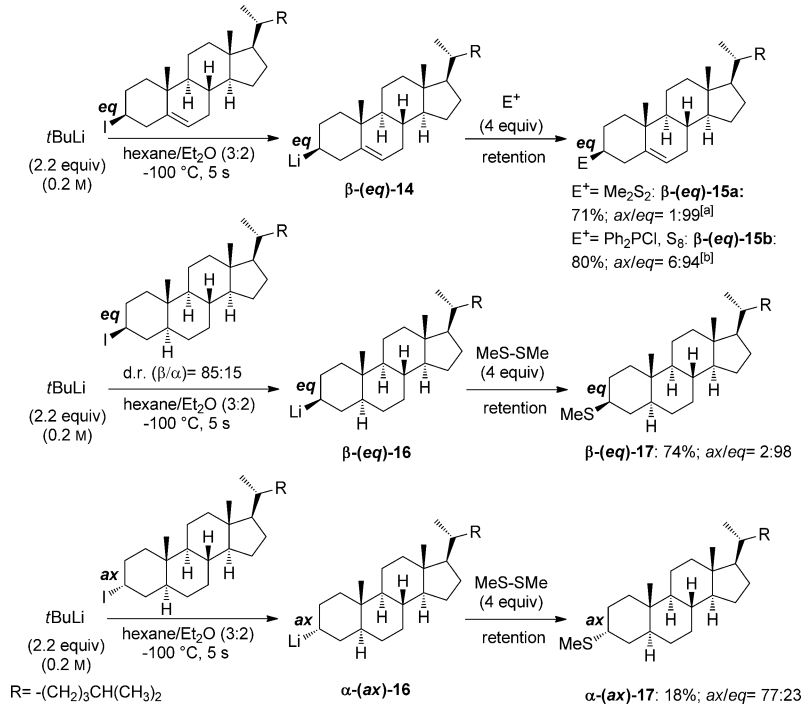
	Li reagent	E^+	Product	Yield [%][a]	d.r.[b]
1	***cis*-(ax)-6c** 	Bu_2S_2	***cis*-(ax)-7e** 	74	91:9
2	***trans*-(ax)-8** 	Bu_2S_2	***trans*-(ax)-9** 	56	89:11
3	**neomen-(ax)-10**	Me_2S_2	**neomen-(ax)-11a** 	23	93:7
4	**neomen-(ax)-10**	Ph_2PCl, S_8	**neomen-(ax)-11b** 	28	91:9[c,d]
5	***cis*-(ax)-12** 	Bu_2S_2	***cis*-(ax)-13**	34	88:12

[a] Yield of isolated product. [b] Axial/equatorial ratio, as determined by capillary GC analysis and ^1H NMR spectroscopy. [c] Determined by ^{31}P NMR spectroscopy. [d] The relative configuration was determined by X-ray crystallography.[14]

cis-configured products ***cis*-(eq)-9a,b** in 63–81% yield and high diastereoselectivity (Table 3, entries 2 and 3). Subjection of menthyl iodide with a diastereomeric purity of 75:25 (menthyl (eq)/neomenthyl (ax)) to the I/Li-exchange reaction mainly resulted in the formation of menthyllithium (**men-(eq)-10**), whose immediate quenching with Me_2S_2 or Ph_2PCl gave menthyl derivatives **men-(eq)-11a,b** with improved diastereoselectivities relative to the starting material (up to 90:10; Table 3, entries 4 and 5). The comparatively low yields (54–59%) can be attributed to the increased basicity of **men-(eq)-10**, which competes more readily with *t*BuLi for deprotonation of the *tert*-butyl iodide (*t*BuI) side-product (cf. Scheme 1), as well as to the presence of 25% neomenthyl iodide in the starting material, which leads to an unstable axial organolithium species (**neomen-(ax)-10**, Table 4).

Next, we examined the substrate scope of the corresponding axially substituted cyclohexyllithium reagents by subjecting their respective stereochemically pure cyclohexyl iodides to the I/Li-exchange conditions (Table 4). Thus, 4-methyl-substituted *cis*-configured cyclohexyllithium ***cis*-(ax)-6c**, which was generated from the corresponding axial iodide, gave, after immediate trapping (5 s) with Bu_2S_2, the expected product, ***cis*-(ax)-7e**, with predominant retention of configuration (d.r. 91:9, 74% yield; Table 4, entry 1). Upon immediate quenching with Bu_2S_2, thermodynamically unstable ***trans*-(ax)-8** gave the expected product, ***trans*-(ax)-9**, in 56% yield and a slightly decreased d.r. (89:11; Table 4, entry 2). Immediate trapping of neomenthyllithium **neomen-(ax)-10**, which was generated from neomenthyl iodide, with Me_2S_2 and Ph_2PCl furnished the axially substituted products with good stereoselectivities (d.r. 91:9 to 93:7), albeit in low yields (23–28%; Table 4, entries 3 and 4). These lower yields are due to a highly reactive neomenthyllithium species, **neomen-(ax)-10**, whose C–Li bond is weakened by steric interactions with the neighboring *i*Pr group. Thus, the higher reactivity of this C–Li bond makes it a better competitor for *t*BuLi in the deprotonation of *t*BuI, which explains the lower yields (cf. Scheme 1). Similar results were obtained in the quenching of *cis*-2-methyl-substituted cyclohexyllithium ***cis*-(ax)-12**: Trapping with Bu_2S_2 led to the product, ***cis*-(ax)-13**, in 34% yield and a good diastereomeric ratio (88:12; Table 4, entry 5), thereby underlining the higher reactivity and greater instability of 2-substituted cyclohexyllithium species with an axial C–Li bond.

The stereochemical behavior of the C–Li bond was observed to be similar in rigid cycloalkyl structures. As shown by Ishihara and co-workers in a related rigid polycyclic ring system, which contained the carbon–iodide bond in an equatorial position, I/Li exchange with *t*BuLi proceeds cleanly and in high yields.[11] Thus, thermodynamically stable cholesteryllithium reagent **β-(eq)-14** was quenched with Me_2S_2 and Ph_2PCl with retention of configuration, thus furnishing the products, **β-(eq)-15a**[14] and **β-(eq)-15b**, in 71–80% yield and high stereoselectivities (d.r. 94:6 to 99:1, Scheme 5). Subjection of cholestanyl iodide with a diastereomeric purity of 85:15 (β/α) to I/Li exchange and subsequent trapping of the resulting lithium compound, **β-(eq)-16**, with Me_2S_2 gave thioether **β-(eq)-17** in 74% yield and a significantly increased diastereomeric ratio (98:2) in favor of the β isomer, owing to fast isomerization of the axial-lithium reagent. This theory was corroborated by our observations on subjecting epicholestanyl iodide to I/Li exchange. The resulting organolithium species, **α-(ax)-16**, was immediately quenched with Me_2S_2 and the axially substituted product, **α-(ax)-17**, was predominantly obtained (α/β, 77:23), albeit in

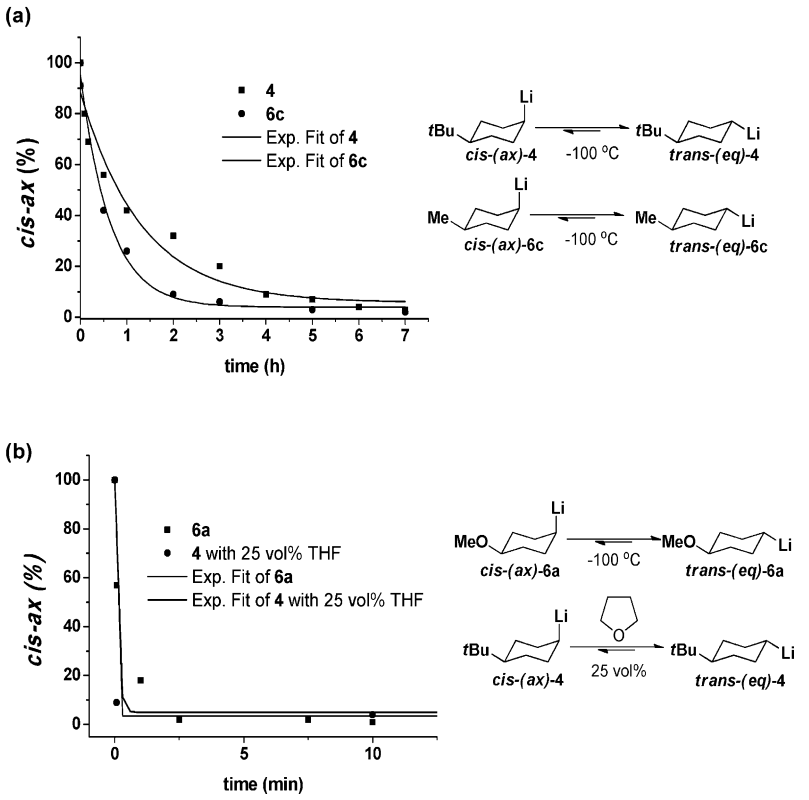


Scheme 5. I/Li exchange on steroid-derived cycloalkyl iodides and the stereochemical behavior of the ensuing organolithium species. [a] The relative configuration was determined by X-ray crystallography.[14] [b] Determined by ^{1}H NMR spectroscopy.

low yield (18%, Scheme 5). Presumably, the large cholestanyl moiety in **α-(ax)-16** hampers the formation of stabilizing oligomeric organolithium clusters (also see the DFT analysis below) and the competitive E_2 elimination occurs much more readily (owing to the availability of a β-hydrogen atom in an *anti*-periplanar conformation).

Next, we followed the kinetics of the invertive equilibration processes under standard conditions at −100 °C for the 4-substituted cyclohexyllithium reagents, ***cis*-(ax)-4** and ***cis*-(ax)-6c**, as well as for ***cis*-(ax)-6a**, which contained a coordinating methoxy group (Scheme 6).

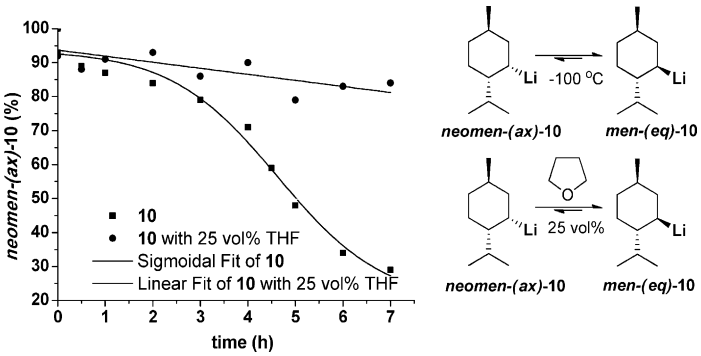
The ratio of axial/equatorial Li species, which was determined by retentive quenching with Me_2S_2 or Bu_2S_2, was recorded over 7 h. A plot of the percentage of the respective axial 4-substituted cyclohexyllithium species versus time resulted in almost-exponential curves for ***cis*-(ax)-4** and ***cis*-(ax)-6c**, which showed that invertive equilibration proceeded with first-order kinetics (Scheme 6a); interestingly, the inversion process was faster for ***cis*-(ax)-6c**, which contained the less-bulky methyl group at the 4-position ($k(\mathbf{4}) = 0.76\ h^{-1}$ versus $k(\mathbf{6c}) = 1.58\ h^{-1}$). Thus, after 2 h, an ax/eq ratio of 9:91 was reached for compound **6c**, whereas 4-*tert*-butyl-substituted cyclohexyllithium (**4**) only equilibrated to a ratio of 32:68 during the same time period. After 7 h, ***cis*-(ax)-4** and ***cis*-(ax)-6c** had been almost completely converted into the thermodynamically more stable diastereomeric Li species ***trans*-(eq)-4** (ax/eq, 3:97) and ***trans*-(eq)-6c** (ax/eq, 2:98). Equilibration towards the more stable equatorially substituted ***trans*-(eq)-6a** proceeded much faster for ***cis*-(ax)-6a**, owing to facilitated C–Li bond breakage through intramolecular coordination of the Li^+ ion to the methoxy moiety (Scheme 6b). In this case, after only 5 s, an ax/eq ratio of 52:48 was



Scheme 6. Kinetics investigation of the equilibration between thermodynamically unstable axial cyclohexyllithium reagents and their stable equatorial diastereomers.

reached. After 2.5 min, ***cis*-(ax)-6a** had almost completely equilibrated into the diastereomeric isomer ***trans*-(eq)-6a** (ax/eq, 2:98). Thus, we wondered whether the addition of THF, which is known to be a strongly coordinating solvent for organolithium species,[17] to ***cis*-(ax)-4** would similarly accelerate its equilibration into the stable ***trans*-(eq)-4**. Indeed, when 25 vol% THF was added to ***cis*-(ax)-4** at −100 °C, immediate quenching with Me_2S_2 already displayed an ax/eq ratio of 9:91. Quenching after 10 min gave ***trans*-(eq)-5a** as the product in 63% yield with a d.r. of 4:96.

When we examined the kinetics of C-Li bond inversion with neomenthyllithium **neomen-(ax)-10** bearing a large *i*Pr-group in the neighboring position, we were surprised to find a completely different behavior (Scheme 7). Its equilibration



Scheme 7. Kinetics investigation of the equilibration between **neomen-(ax)-10** and **men-(eq)-10**, with and without the addition of THF.

followed a sigmoidal curve. Thus, inversion was very slow during the first 4 h reaching only an ax/eq-ratio of 71:29. Then, the slope of the curve fell more steeply showing an accelerated inversion resulting in an ax/eq-ratio of 29:71 after 7 h.

This hints towards an autocatalytic process in which menthyllithium **men-(eq)-10** promotes its own formation.[18] With enough **men-(eq)-10** (ca. 30%) formed, inversion accelerates. However, the overall inversion proceeds much slower than for the 4-substituted cyclohexyllithiums. Almost complete inversion from **neomen-(ax)-10** to **men-(eq)-10** could be achieved when the reaction mixture was warmed, directly after I-Li exchange on neomenthyl iodide, from −100 °C to −60 °C within 50 min. Quenching of the lithium reagent with Me_2S_2 gave **men-(eq)-11a** with a high stereoselectivity (ax/eq = 2:98) and 32% yield. Notably, addition of 25 vol% of THF did not speed up the equilibration at −100 °C. Instead, the ax/eq-ratio changed much more slowly over time. In this case, the kinetics were best described by a straight line. After 7 h, the ax/eq-ratio had only dropped to 84:16. In order to explore the preference of lithium for the equatorial over the axial positions in cyclohexane ring systems, theoretical studies have been performed for 4-*tert*-butylcyclohexyllithium **4** in its equatorial (***trans*-(eq)-4**) and axial (***cis*-(ax)-4**) configurations.

Following earlier theoretical work on organolithium species,[19] geometry optimizations were performed at the B3LYP/6-31+G(d) level of theory. Then, improved enthalpies and free energies at 298.15 K, as reported in Table 5, were obtained at the MP2(FC)/6-311+G(2d,p)//B3LYP/6-31+G(d) level of theory. Interestingly, a comparison of the gas-phase stabilities of monomeric ***trans*-(eq)-4** and ***cis*-(ax)-4** indicated a small thermodynamic preference for axially substituted ***cis*-(ax)-4** (by 3.8 kJ mol^{-1}; Table 5, entry 1). This energy difference remains essentially unchanged, even at higher levels of theory, such as G3+(MP2)B3 (see the Supporting Information).

How far this small preference for the axial position depends on the state of solvation was subsequently tested by the inclusion of up to three explicit THF molecules in the calculations. The strongly coordinating THF (rather than weakly coordinating Et_2O or even mixtures of Et_2O and *n*-hexane) was used in the calculations, with the logic that possible solvent effects should be magnified and, thus, clearly recognizable. However, somewhat surprisingly, the explicit coordination of THF molecules to the lithium atom does not lead to the expected large preference for the equatorial isomer of compound **4** and, in fact, the following equatorial/axial energy differences are obtained: −8.2 (1 THF), −3.6 (2 THF) and +0.5 (3 THF molecules), where a negative sign implies a larger stability of the axial isomer. The additional consideration of bulk solvation effects, which were not described properly through the inclusion of three explicit THF molecules in the SMD continuum model, brought the equatorial/axial energy difference to −3.1 kJ mol^{-1} in preference of the axial isomer ***cis*-(ax)-4**. This result implies that, even in the presence of a strongly coordinating solvent, such as

Table 5. Relative gas-phase stabilities of monomeric and dimeric compound **4** and hexameric compound **18**.

Entry	Structures[a]		$\Delta G_{298/ax-eq}$ [kJ mol^{-1}][b]
1	*trans*-(eq)-4	*cis*-(ax)-4	−3.8
2	*trans*-(eq)-4(THF)$_3$	*cis*-(ax)-4(THF)$_3$	+0.5
3	(*trans*-(eq)-4)$_2$	(*cis*-(ax)-4)$_2$	+4.7
4	(*trans*-(eq)-18)$_6$	(*cis*-(ax)-18)$_6$	+71.3

[a] The geometries were optimized at the B3LYP/6-31+G(d) level in all cases. [b] Energies were determined at the MP2(FC)/6-311+G(2d,p) level.

THF, in which the lithium atom can safely be assumed to completely fill its first coordination shell, no large preference for equatorial isomer ***trans*-(eq)-4** can be found. However, this result is in clear contrast to the trapping experiments performed at −100 °C in Et_2O/hydrocarbon solvents, thus demonstrating a large or exclusive preference for equatorial isomers. Because the experimentally observed strong stereochemical preference for equatorially substituted ***trans*-(eq)-4** may be due to aggregates that are formed at low temperatures in weakly coordinating solvents, calculations were also performed on the respective cyclohexyllithium aggregates. A comparison of the gas-phase stabilities of dimers **(*trans*-(eq)-4)$_2$** and **(*cis*-(ax)-4)$_2$** only shows a small preference (4.72 kJ mol^{-1}) for the equatorial isomer (Table 5, entry 3). The hexameric structures found for *n*BuLi[20] (from *n*-hexane) and cyclohexyllithium[21] (from benzene) indicate that even-higher aggregates can easily be formed in less-polar solvents. Therefore, equatorial/axial preference was also explored for the hexameric form of cyclohexyllithium. Despite the fact that this system now lacks the *t*Bu anchor at the 4-position of the cyclohexane ring, nevertheless, these results are expected to be relevant to the substituted system. The results obtained at the B3LYP or MP2 levels of theory are quite clear about the strong preference for the all-equatorial isomer, **(*trans*-(eq)-18)$_6$**, over the all-axial isomer, **(*cis*-(ax)-18)$_6$**, in agreement with the conformation found in the hexameric X-ray crystal structure.[21] The large energy difference of 71.3 kJ mol^{-1} in favor of **(*trans*-(eq)-18)$_6$** implies a preference of 11.9 kJ mol^{-1} for the equatorial orientation in each of the six monomers (Table 5, entry 4). Compared to the equatorial/axial energy differences for the respective *tert*-butyl-cyclohexyllithium monomers (***trans*-(eq)-4** and ***cis*-(ax)-4**) and dimers ((**(*trans*-(eq)-4)$_2$** and **(*cis*-(ax)-4)$_2$**), this result implies that the state of aggregation may be a key determinant for the stereochemical preference in substituted cyclohexyllithiums.

Conclusion

In summary, we have described a practical preparation of stereodefined cyclic secondary alkyllithium reagents from their corresponding organic iodides. This stereoretentive method allowed a detailed study of the thermodynamic stabilities, stereochemical behavior, and reactivities of a wide range of axially and equatorially substituted cyclohexyllithium reagents.

Thus, it was possible to stereospecifically synthesize various *cis*- and *trans*-cyclohexane derivatives by quenching with several classes of electrophiles. We also found a clear tendency of equilibration towards the equatorially substituted lithium compounds. This thermodynamic phenomenon can be explained by the formation of highly aggregated organolithium species that display a large energy difference between the all-equatorial and all-axial species, as confirmed by ab initio calculations. Polar solvents, such as THF, sped up the equilibration process for axial 4-substituted cyclohexyllithium reagents, whereas they displayed a stabilization effect on 2-substituted neomenthyllithium **neomen-(ax)-10**. An invertive reactivity pathway was found for the reaction of thermodynamically less-stable axially substituted cyclohexyllithium ***cis*-(ax)-4** with organotin halides.

Experimental Section

Preparation of *cis*-(ax)-1: A 1.0 M solution of I_2 (1.2 equiv, 15.2 g, 60 mmol) in CH_2Cl_2 (60 mL) was prepared in a flame-dried, Ar-flushed Schlenk flask that was equipped with a stirrer bar and the solution was cooled to 0 °C by using a Huber T100 cryostat. PPh_3 (1.2 equiv, 15.7 g, 60 mmol) was added portion-wise and the resulting suspension was stirred for 1 h, before *N*-methyl-imidazole (1.2 equiv, 4.79 mL, 60 mmol) was added. The reaction mixture became a bright-yellow suspension and *trans*-4-(*tert*-butyl)cyclohexanol (1.0 equiv, 7.81 g, 50 mmol) was added portion-wise. The resulting mixture was stirred for 15 h at 0 °C, before being quenched with a saturated solution of $NaHSO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed on a rotary evaporator (35 °C, 8 mbar, <30 min). The crude mixture was purified by column chromatography on silica gel (*i*-hexane), the solvents were removed on a rotary evaporator (35 °C, 8 mbar, <30 min), and the product was placed under high vacuum (×10^{-3} mbar) at 30 °C to remove cyclohexene and any elimination by-products. Neat *cis*-1-(*tert*-butyl)-4-iodocyclohexane (***cis*-(ax)-1**) was obtained as a white solid (7.5 g, 56 % yield, d.r. 98:2). ^{1}H NMR (599 MHz, $CDCl_3$): δ = 4.89 (br s, 1H), 2.13 (d, J = 14.0 Hz, 2H), 1.68–1.62 (m, 2H), 1.60–1.47 (m, 4H), 1.08 (tt, ^1J = 11.5 Hz, ^2J = 3.3 Hz, 1H), 0.90 ppm (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.8, 37.9, 36.9, 32.6, 27.4, 23.3 ppm; IR (ATR): $\tilde{\nu}$ = 2956 (s), 2939 (vs), 2921 (m), 2885 (m), 2863 (m), 2845 (m), 2832 (m), 1482 (w), 1472 (w), 1444 (w), 1430 (m), 1418 (m), 1390 (w), 1366 (m), 1350 (w), 1308 (m), 1243 (m), 1232 (m), 1186 (s), 1016 (m), 996 (m), 851 (m), 764 (w), 652 nm (m); MS (70 eV, EI): *m*/*z* (%): 266 (8) [*M*]$^+$, 140 (11), 139 (100), 123 (15), 83 (47), 81 (21), 69 (17), 67 (18), 57 (69), 55 (17), 41 (14); HRMS (EI): *m*/*z* calcd for $C_{10}H_{19}I$: 266.0531; found: 266.0530.

Preparation of *cis*-(ax)-5a: A solution of *n*-hexane /Et_2O (3:2, 5.5 mL) was prepared in a flame-dried, Ar-flushed Schlenk flask that was equipped with a stirrer bar and the solution was cooled to −100 °C by using a Huber T100 cryostat. *t*BuLi (2.2 equiv, 1.3 M in *n*-hexane, 0.84 mL, 1.1 mmol) was added by syringe. After 5 min, a 1.0 M solution of *cis*-4-*tert*-butyl-cyclohexyl iodide (***cis*-(ax)-1**, 1.0 equiv, 134 mg, 0.5 mmol) in *n*-hexane/Et_2O (3:2, 0.5 mL) was added. The reaction mixture was quenched after 4–5 s with neat S_2Me_2 (4 equiv, 0.18 mL, 2 mmol). After stirring for 5 min at −100 °C, a saturated aqueous solution of NH_4Cl (2 mL) was added. After warming to RT, the phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phase was dried over Na_2SO_4 and the solvents were evaporated. Purification of the crude oil by column chromatography on silica gel (*i*-hexane) provided thioether ***cis*-(ax)-5a** (68 mg, 73 % yield, d.r. 90:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (br s, 1H), 2.06 (s, 3H), 1.95 (d, J = 14.1 Hz, 2H), 1.66 (tt, ^1J = 13.4 Hz, ^2J = 3.7 Hz, 2H), 1.59–1.49 (m, 2H), 1.49–1.34 (m, 2H), 1.07–0.96 (m, 1H), 0.86 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.4, 44.3, 32.6, 31.1, 27.5, 21.9, 14.8 ppm; IR (ATR): $\tilde{\nu}$ = 2938 (vs), 2930 (vs), 2864 (m), 2846 (m), 1478 (m), 1467 (m), 1440 (m), 1393 (w), 1365 (s), 1312 (m), 1263 (m), 1237 (w), 1227 (w), 1214 (m), 1024 (w), 865 (w), 770 (w); MS (70 eV, EI): *m*/*z* (%): 186 (8) [*M*]$^+$, 175 (28), 147 (25), 83 (10), 57 (22); HRMS (EI): *m*/*z* calcd for $C_{11}H_{22}S$: 186.1442; found: 186.1443.

Preparation of *trans*-(eq)-5a: A solution of *n*-hexane/Et_2O (3:2; 5.5 mL) was prepared in a flame-dried, Ar-flushed Schlenk tube that was equipped with a stirrer bar and the solution was cooled to −100 °C by using a Huber T100 cryostat. *t*BuLi (2.2 equiv, 1.3 M in *n*-hexane 0.84 mL, 1.1 mmol) was added by syringe. After 5 min, a 1.0 M solution of *trans*-4-*tert*-butyl-cyclohexyl iodide (***trans*-(eq)-1**, 1.0 equiv, 134 mg, 0.5 mmol) in

hexane/Et_2O (3:2, 0.5 mL) was added. The reaction mixture was quenched after 4–5 s with neat S_2Me_2 (4 equiv, 0.18 mL, 2 mmol). After stirring for 5 min at −100 °C, a saturated aqueous solution of NH_4Cl (2 mL) was added. After warming to RT, the phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phase was dried over Na_2SO_4 and the solvents were evaporated. Purification of the crude oil by column chromatography on silica gel (*i*hexane) provided thioether ***trans*-(eq)-5a** (84 mg, 90% yield, d.r. 9:91). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (tt, ^1J = 12.0 Hz, ^2J = 3.6 Hz, 1H), 2.09 (s, 3H), 2.06 (br s, 1H), 1.84 (d, J = 10.0 Hz, 2H), 1.36–1.15 (m, 3H), 1.13–0.96 (m, 3H), 0.85 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.5, 44.9, 33.7, 32.4, 27.6, 27.5, 13.1 ppm; IR (ATR): $\tilde{\nu}$ = 2936 (vs), 2856 (s), 1478 (m), 1467 (m), 1448 (m), 1394 (w), 1365 (s), 1275 (w), 1235 (w), 1230 (w), 1211 (w), 1174 (w), 1038 (w), 1013 (m), 1006 (m), 970 (w), 954 (w), 897 (w); MS (70 eV, EI): m/z (%): 186 (100) $[M]^+$, 175 (89), 138 (49), 129 (55), 123 (48), 95 (54), 83 (55), 82 (40), 81 (87), 69 (32), 67 (31), 57 (92), 55 (35), 41 (32); HRMS (EI): m/z calcd for $C_{11}H_{22}S$: 186.1442; found: 186.1432.

Preparation of *cis*-(ax)-7d: A solution of *n*-hexane/Et_2O (3:2; 5.5 mL) was prepared in a flame-dried, Ar-flushed Schlenk tube that was equipped with a stirrer bar and the solution was cooled to −100 °C by using a Huber T100 cryostat. *t*BuLi (2.2 equiv, 1.3 M in *n*-hexane, 0.84 mL, 1.1 mmol) was added by syringe. After 5 min, a 1.0 M solution of ((*cis*-4-iodocyclohexyl)oxy)triisopropylsilane (1.0 equiv, 191 mg, 0.5 mmol) in *n*-hexane/Et_2O (3:2, 0.5 mL) was added. The reaction mixture was quenched after 4–5 s with neat $EtSO_2Cl$ (4 equiv, 0.19 mL, 2 mmol). After stirring for 5 min at −100 °C, a saturated aqueous solution of NH_4Cl (2 mL) was added. After warming to RT, the phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phase was dried over Na_2SO_4 and the solvents were evaporated. Purification of the crude oil by column chromatography on silica gel (*i*hexane) provided cyclohexyl chloride ***cis*-(ax)-7d** (81 mg, 56% yield, d.r 94:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (tt, ^1J = 8.8 Hz, ^2J = 3.6 Hz, 1H), 3.91–3.88 (m, 1H), 2.10–2.01 (m, 2H), 1.88–1.78 (m, 4H), 1.59–1.51 (m, 2H), 1.04–1.03 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.9, 59.5, 32.8, 29.9, 18.3, 12.5 ppm; IR (ATR): $\tilde{\nu}$ = 2942, 2866, 1463, 1368, 1258, 1116, 1049, 1017, 995, 882, 810, 679; MS (70 eV, EI): m/z (%):290 (4) $[M]^+$, 249 (75), 247 (100), 131 (24), 103 (2), 81 (43), 61 (18); HRMS (EI): m/z calcd for $C_{15}H_{31}ClOSi$: 290.1833; found: 290.1839.

Preparation of *trans*-(eq)-7d: A solution of *n*-hexane/Et_2O (3:2, 5.5 mL) was prepared in a flame-dried, Ar-flushed Schlenk tube that was equipped with a stirrer bar and the solution was cooled to −100 °C by using a Huber T100 cryostat. *t*BuLi (2.2 equiv, 1.3 M in *n*-hexane, 0.84 mL, 1.1 mmol) was added by syringe. After 5 min, a 1.0 M solution of ((*trans*-4-iodocyclohexyl)oxy)triisopropylsilane (1.0 equiv, 191 mg, 0.5 mmol) in *n*-hexane/Et_2O (3:2, 0.5 mL) was added. The reaction mixture was quenched after 4–5 s with neat $EtSO_2Cl$ (4 equiv, 0.19 mL, 2 mmol). After stirring for 5 min at −100 °C, a saturated aqueous solution of NH_4Cl (2 mL) was added. After warming to RT, the phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phase was dried over Na_2SO_4 and the solvents were evaporated. Purification of the crude oil by column chromatography on silica gel (*i*hexane) provided cyclohexyl chloride ***trans*-(eq)-7d** (89 mg, 61% yield, d.r. 1:99). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10–4.06 (m, 1H), 3.88–3.84 (m, 1H), 2.22–2.15 (2H), 1.98–1.91 (m, 2H), 1.70–1.60 (m, 2H), 1.50–1.41 (m, 2H), 1.03–1.02 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.5, 59.7, 32.7, 29.9, 18.3, 12.5 ppm; IR (ATR): $\tilde{\nu}$ = 2943, 2865, 1463, 1375, 1255, 1104, 1014, 881, 827, 814, 738, 677; MS (70 eV, EI): m/z (%): 290 (2) $[M]^+$, 249 (36), 248 (18), 247 (100), 131 (12), 103 (24), 81 (44), 75 (22), 61 (10); HRMS (EI): m/z calcd for $C_{15}H_{31}ClOSi$: 290.1833; found: 290.1844.

Acknowledgements

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[13] With *trans*-iodide ***trans*-(eq)-1**, the conventional addition procedure affords the expected lithium reagent, ***trans*-(eq)-4**, in 20–30% lower yield than with the inverse-addition procedure (also see Scheme 2 and the Supporting Information).

[14] CCDC-890872 (**β-(eq)-15a**), CCDC-890873 (***cis*-(ax)-1**), CCDC-890874 (**neomen-(ax)-11b**), and CCDC-890875 (***trans*-(eq)-5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] Overall retention was observed. We could also envisage a double inversion (for example, inversion in the I/Li-exchange step and inversion in the reaction of the lithium reagent with the electrophile). In accordance with the work of Glaze et al. (see ref. [9b,c]), who showed that the thermodynamically more stable cyclohexyllithiums were their *trans* isomers, we disfavored the double-inversion pathway. I/Li exchange is presumed to proceed through the formation of an "ate" intermediate, which subsequently converts into the organolithium species. For references, see: a) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101–4103; b) see also ref. [10h.].

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