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Lithium Reagents

Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters

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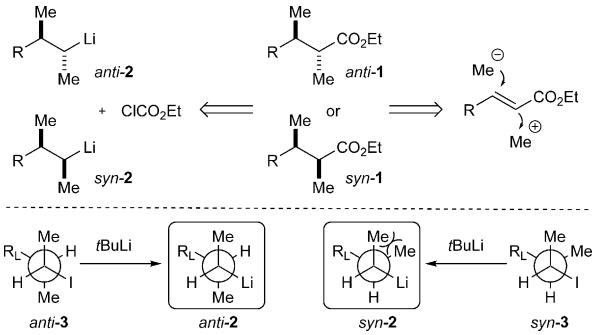
Abstract: The treatment of α-chiral secondary alkyl iodides with *t*BuLi at −100 °C leads to the corresponding secondary alkyllithiums with high retention of configuration. Subsequent quenching with various electrophiles such as Bu_2S_2, DMF, $MeOB(OR)_2$, or Et_2CO provides the desired products with retention of configuration. Furthermore, a transmetalation with $CuBr{\cdot}P(OEt)_3$ also allows retentive trapping with acid chlorides and ethylene oxide. The quenching of the resulting alkyllithiums with $ClCO_2Et$ furnishes stereoselectively *syn*- and *anti*-ethyl-2,3-dimethyl ester carboxylates (d.r. > 94%). Related esters bearing three adjacent stereo-controlled centers (stereotriads) have also been prepared. This method has been applied to the synthesis of the ant pheromone (±)-lasiol in 26% overall yield (four steps) with d.r. = 97:3 starting from commercially available *cis*-2,3-epoxybutane.

The preparation of chiral organometallic building blocks is useful for the stereoselective construction of acyclic natural products bearing several adjacent chiral centers.[1] For example, the diastereoselective synthesis of 2,3-dimethylcarboxylate derivatives of type **1**, encountered in complex natural products,[2] may be performed using a diastereoselective 1,4-addition/alkylation. This retrosynthesis has often been used but has several drawbacks, such as the degree of diastereoselectivity, and access to both *anti*- and *syn*-isomers of **1**.[2] Alternatively, one can envision the use of a carboxylation of the chiral organolithium reagents of type **2** with $ClCO_2Et$ for preparing esters of type **1** stereoselectively (Scheme 1). Although acyclic heteroatom-stabilized chiral lithium reagents are well known,[3,4] non-stabilized secondary alkyllithiums have been less extensively studied.[3c] Recently, we reported that an I–Li-exchange allows the generation of functionalized secondary alkyllithium reagents bearing remote functionalities (at position 3 or 4).[5] Stereoselective transmetalations further extend the synthetic scope of these organometallic intermediates.[6]



Scheme 1. The retrosynthetical analysis of *anti*- and *syn*-2,3-dimethylcarboxylate derivatives (**1**) (top), and diastereoselective generation of α-chiral *anti*- and *syn*-secondary alkyllithiums (**2**) from the secondary alkyl iodides (**3**) (bottom).

Here, we wish to report a highly stereoselective preparation of various α-chiral alkyllithiums of type **2** starting from the corresponding iodides, and their application to the stereoselective preparation of 2,3-dimethylcarboxylates of type **1**. We have also extended this method to the preparation of chiral lithium derivatives bearing three adjacent stereocenters (stereotriads).[7]

Thus, the treatment of diastereomerically enriched *anti*-alkyl iodide (*anti*-**3a**, d.r. = 98:2) with *t*BuLi (inverse addition) in hexane:ether (3:2) at −100 °C (5 min) provides the intermediate lithium reagent (*anti*-**2a**) (Scheme 2). This isomer was trapped with Bu_2S_2[5] (2 equiv, −100 °C, 10 s) leading to the *anti*-thioether (*anti*-**4a**) in 61% yield and with d.r. = 96:4, showing a high retention of the configuration.[5b] Similarly, the reaction of the secondary alkyl iodide (*syn*-**3a**, d.r. = 2:98) with *t*BuLi, under the same conditions, followed by quenching with Bu_2S_2, gives the *syn*-thioether (*syn*-**4a**) in 81% yield and d.r. = 4:96, indicating again a high retention for this electrophilic substitution.

This reaction sequence was extended to other electrophiles such as MeOBpin[5b,c] (MeOBpin = 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane) leading to the boronic esters (*anti*-**4b** and *syn*-**4b**,[8] entries 1 and 2 of Table 1) in 60 and 83% yield, as well as 98 and 99% retention of configuration, respectively.[9] Reactions of the lithium reagents *anti*-**2a** and *syn*-**2a** with DMF[5b,c] produced the *anti*- and *syn*-aldehydes (*anti*-**4c** and *syn*-**4c**, entries 3 and 4) in 60 and 70% yield with 93 and 95% retention of configuration, respectively. The preparation of tertiary alcohols *anti*-**4d** (d.r. = 97:3, 71% yield) and *syn*-**4d** (d.r. = 8:92, 50% yield) was achieved by the addition of alkyl-

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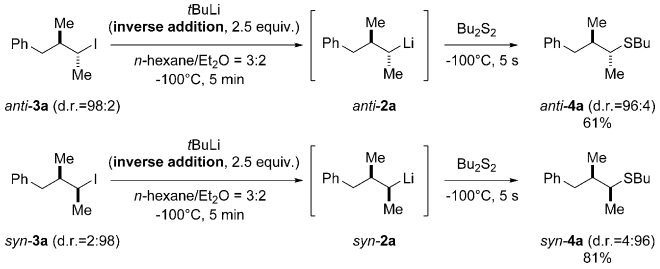
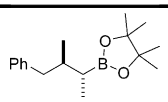
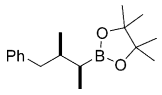
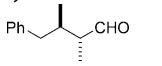
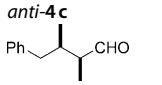
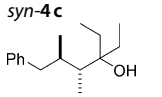
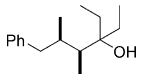
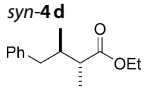
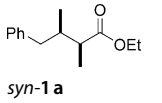


Scheme 2. Stereoselective preparation of *anti*- and *syn*-thioethers (*anti*-**4a** and *syn*-**4a**) from corresponding *anti*- and *syn*-alkyl iodides (*anti*-**3a** and *syn*-**3a**, respectively), through I–Li-exchange and subsequent trapping with Bu_2S_2.

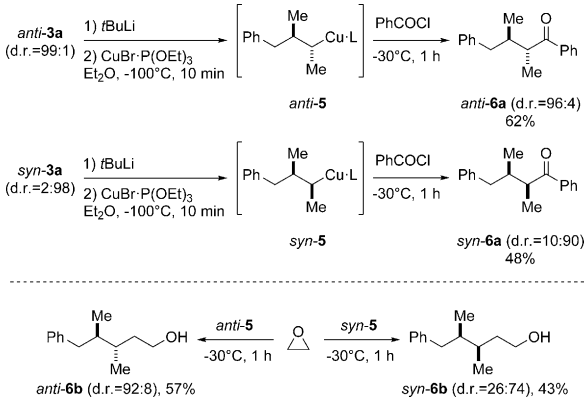
lithiums *anti*-**2a** and *syn*-**2a** to Et_2CO, respectively.[3f,5b,c,10] Most importantly, the use of $ClCO_2Et$[5b,c] as an electrophile in this sequence afforded the ethyl-2,3-dimethylcarboxylic esters *anti*-**1a** (d.r. = 97:3) and *syn*-**1a** (d.r. = 9:91) in 75 and 82% yields (entries 7 and 8), respectively. In all cases, high levels of retentive substitutions were found (> 94% retention).[9]

The electrophile scope can be further extended using a transmetalation with the hexane-soluble copper complex CuBr·$P(OEt)_3$ (Scheme 3).[11] The resulting secondary alkylcopper reagent (*anti*-**5**) obtained from the alkyl iodide (*anti*-**3a**, d.r. = 99:1) gives after acylation with PhCOCl the *anti*-ketone (*anti*-**6a**) in 62% yield and d.r. = 96:4. Similarly, the *syn*-iodide (*syn*-**3a**, d.r. = 2:98) undergoes a smooth I–Li-exchange and, after transmetalation with CuBr·$P(OEt)_3$, leads to the copper reagent (*syn*-**5**). Benzoylation of *syn*-**5** affords the *syn*-ketone (*syn*-**6a**) in 48% yield (d.r. = 10:90; Scheme 3). Interestingly, the retentive transmetalation to copper also allows the opening of ethylene oxide[12] with *anti*- and *syn*-**5**. In the case of the less sterically hindered copper reagent (*anti*-**5**), a satisfying retention is observed in the formation of the alcohol *anti*-**6b** (d.r. = 92:8, 57% yield). However, in the case of the more sterically congested *syn*-**5** (compare with Scheme 1), an erosion of the diastereoselectivity was observed and the desired alcohol *syn*-**6b** was obtained in 43% yield with a moderate d.r. of 26:74. This lower diastereoselectivity can be explained by the somewhat lower reactivity of ethylene oxide, leading to a competitive configurational isomerization of *syn*-**5** (Scheme 3).[12]

Table 1. Diastereoselective reactions of *anti*- and *syn*- acyclic secondary alkyllithium **2a** with electrophiles leading to products of type **4** and **1**.

Entry	Li-reagent (d.r)[a]	Electrophile	Product	Yield [%] (d.r.)[b]
1	*anti*-**2a** (99:1)	MeOBpin	 *anti*-**4b**	83 (99:1)
2	*syn*-**2a** (5:95)	MeOBpin	 *syn*-**4b**	60 (6:94)
3	*anti*-**2a** (99:1)	DMF	 *anti*-**4c**	60 (95:5)
4	*syn*-**2a** (1:99)	DMF	 *syn*-**4c**	70 (7:93)
5	*anti*-**2a** (99:1)	EtCOEt	 *anti*-**4d**	71 (97:3)
6	*syn*-**2a** (2:98)	EtCOEt	 *syn*-**4d**	50 (8:92)
7	*anti*-**2a** (99:1)	$ClCO_2Et$	 *anti*-**1a**	82 (97:3)
8	*syn*-**2a** (5:95)	$ClCO_2Et$	 *syn*-**1a**	75 (9:91)

[a] Diastereomeric ratio of the corresponding iodides (*anti*-**3a** and *syn*-**3a**) given in parentheses. [b] The diastereomeric ratio was determined by NMR analysis.



Scheme 3. Stereoselective formation of alkylcopper reagents *anti*-**5** and *syn*-**5** from the alkyl iodides *anti*-**3a** and *syn*-**3a**, respectively, through I–Li-exchange, transmetalation with CuBr·$P(OEt)_3$, and subsequent reactions with electrophiles.

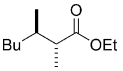
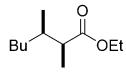
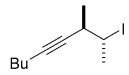
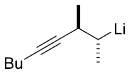
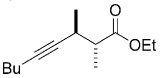
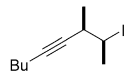
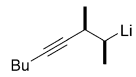
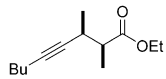
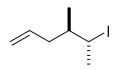
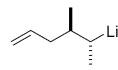
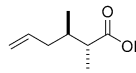
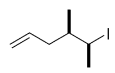
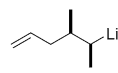
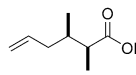
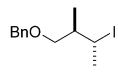
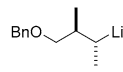
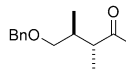
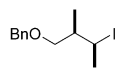
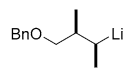
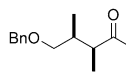
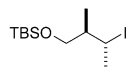
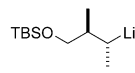
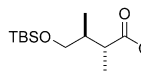
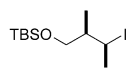
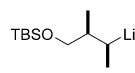
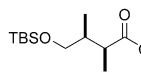
With this method in hand, we have prepared a range of both *anti*- and *syn*-2,3-dimethyl-substituted carboxylates of type **1** starting from readily available alkyl iodides of type **3**.[14] Thus, the *anti*-alkyllithium (**2b**), prepared from the corresponding alkyl iodide (*anti*-**3b**, d.r. = 99:1), was treated at −100 °C under standard conditions with $ClCO_2Et$ leading to the *anti*-ethyl-2,3-dimethylcarboxylate (*anti*-**1b**) in 86% yield and d.r. = 97:3 (Table 2, entry 1). Similarly, the *syn*-alkyl iodide (*syn*-**3b**, d.r. = 1:99) was converted by this sequence to the *syn*-2,3-dimethylcarboxylate (*syn*-**1b**) in 63% yield and d.r. = 5:95 (entry 2). Several additional functionalities such as a triple bond or double bond are perfectly tolerated, as well as a protected hydroxyl group. For example, the *anti*-alkyl iodide (*anti*-**3c**, d.r. = 99:1) bearing a triple carbon–carbon bond in the γ-position was converted to the corresponding *anti*-ethyl-2,3-dimethylcarboxylic ester (*anti*-**1c**) in 72% yield and d.r. = 97:3 (entry 3). The other diastereomer (*syn*-**1c**) was obtained from the *syn*-alkyl iodide (*syn*-**3c**, d.r. = 1:99) under the same condi-

tions in 61% yield and d.r. = 1:99 (entry 4). The treatment of *anti*-alkyl iodide (*anti*-**3 d**, d.r. = 97:3) containing a remote double bond with *t*BuLi under standard conditions afforded the *anti*-alkyllithium **2 d**, which was then treated with $ClCO_2Et$ to provide the *anti*-carboxylic derivative (*anti*-**1 d**) in 64% yield and d.r. = 96:4 (entry 5). A lower retention of configuration was observed in the preparation of the *syn*-carboxylate **1 d** from the *syn*-alkyl iodide (*syn*-**3 d**, d.r. = 5:95). Thus, the ester (*syn*-**1 d**) was isolated in 69% yield with d.r. = 9:91 (entry 6). The *anti*- and *syn*-benzyloxy-protected alkyl iodides (*anti*-**3 e**, d.r. = 96:4; and *syn*-**3 e**, d.r. = 5:95) were converted to the corresponding *anti*- and *syn*-carboxylic esters (*anti*-**1 e** and *syn*-**1 e**) in the same manner in 77 and 60% yield (d.r. = 91:9 and d.r. = 10:90; entries 7 and 8), respectively. The *anti*- and *syn*- alkyl iodides bearing an OTBS-group (TBS = *tert*-butyldimethylsilyl) at the γ-position (*anti*-**3 f**, d.r. = 97:3; and *syn*-**3 f**, d.r. = 5:95) were treated under the same conditions to afford *anti*-**2 f** and *syn*-**2 f**, both of which reacted with $ClCO_2Et$ leading to the ethyl-2,3-dimethylcarboxylic esters *anti*-**1 f** in 72% yield with d.r. = 94:6, and *syn*-**1 f** in 59% yield and d.r. = 8:92 (entries 9 and 10, respectively). Thus, in all cases the retention is higher than 94%. The best results are obtained from *anti*-lithium reagents, whereas the *syn*-alkyllithiums, which are more sterically congested (Scheme 1) and less configurationally stable, lead to somewhat lower diastereoselectivities (Table 2, entries 2, 6, 8, and 10).

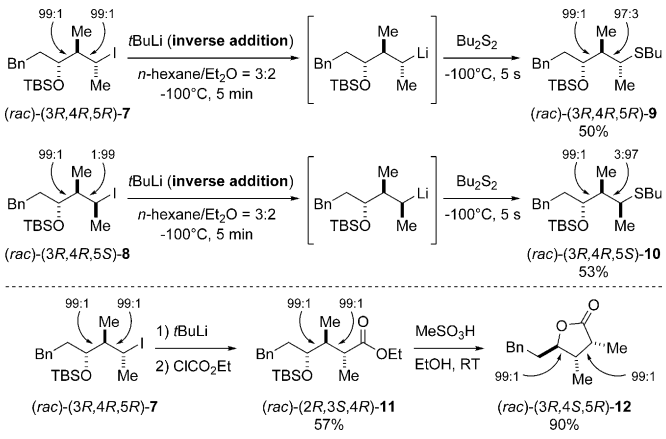
Our approach can be extended to the preparation of stereotriads.[7] Thus, the reaction of the two diastereomeric alkyl iodides **7** and **8** bearing three adjacent stereocenters are converted with retention of configuration through an I–Li-exchange, followed by a quenching with Bu_2S_2, which leads to the thioethers **9** and **10** in 50 and 53% yield and diastereoselectivities of 97:3 and 3:97, respectively (Scheme 4). As an application, the alkyl iodide **7** was transformed into the corresponding ethyl ester **11** (by reaction with *t*BuLi and then $ClCO_2Et$) with 57% overall yield and d.r. = 99:1. The lactonization of **11** furnishes the lactone **12** in 90% yield and d.r. = 99:1[14] (Scheme 4).

We have also prepared an ant sex pheromone, (±)-lasiol[15] (alcohol **13**), in four steps and 26% overall yield starting from

Table 2. Diastereoselective synthesis of *anti*- and *syn*-ethyl-2,3-dimethyl carboxylates **1 b–f** from the alkyl iodides **3 b–f** by I–Li-exchange and following trapping with $ClCO_2Et$ after 5 seconds.

Entry	Iodide[a]	Li-reagent	Product and Yield[a]
1			
	anti-**3 b** (99:1)	*anti*-**2 b**	*anti*-**1 b**, 86% (97:3)
2			
	syn-**3 b** (1:99)	*syn*-**2 b**	*syn*-**1 b**, 63% (5:95)
3			
	anti-**3 c** (99:1)	*anti*-**2 c**	*anti*-**1 c**, 72% (97:3)
4			
	syn-**3 c** (1:99)	*syn*-**2 c**	*syn*-**1 c**, 61% (1:99)
5			
	anti-**3 d** (97:3)	*anti*-**2 d**	*anti*-**1 d**, 64%, (96:4)
6			
	syn-**3 d** (5:95)	*syn*-**2 d**	*syn*-**1 d**, 69% (9:91)
7			
	anti-**3 e** (96:4)	*anti*-**2 e**	*anti*-**1 e**, 77% (91:9)
8			
	syn-**3 e** (5:95)	*syn*-**2 e**	*syn*-**1 e**, 60% (10:90)
9			
	anti-**3 f** (97:3)	*anti*-**2 f**	*anti*-**1 f**, 72% (94:6)
10			
	syn-**3 f** (5:95)	*syn*-**2 f**	*syn*-**1 f**, 59% (8:92)

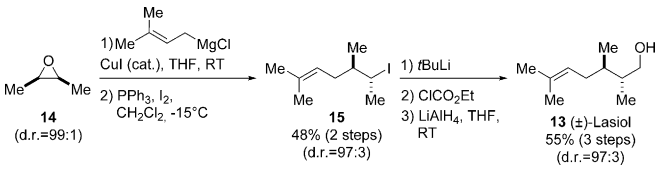
[a] The diastereomeric ratio, given in parentheses, was determined by NMR analysis.



Scheme 4. Stereoselective synthesis of stereotriads.

the commercially available *cis*-2,3-epoxybutane **14**. First, epoxide opening with prenylmagnesium chloride[16] in the presence of CuI,[12c,17] followed by an Appel reaction[5,18] furnishes the secondary alkyl iodide **15** in 48% yield (d.r. = 97:3, Scheme 5).[19] The alkyl iodide **15** was converted to (±)-lasiol (**13**) in three more steps : I–Li-exchange, quenching with $ClCO_2Et$, followed by $LiAlH_4$ reduction provided (±)-lasiol (**13**) in 55% overall yield and d.r. = 97:3.

In summary, we have reported a retentive I–Li-exchange reaction of α-chiral secondary iodides leading to chiral secondary alkyllithium building blocks, which were used to prepare various 2,3-dimethyl carboxylic ester derivatives often encountered in natural product targets with high diastereoselectivity. We have extended our method to the stereoselective preparation



Scheme 5. Diastereoselective synthesis of (±)-lasiol (**13**) from *cis*-2,3-epoxybutane (**14**).

of carboxylic derivatives bearing stereotriads, and have also prepared the sex ant pheromone (±)-lasiol. Further applications are currently being investigated in our laboratory.

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Keywords: carboxylic acids · copper · lithium · pheromone · stereotriads

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[19] The other diastereomer was prepared to estimate the diastereomeric ratio. (See Supporting Information).

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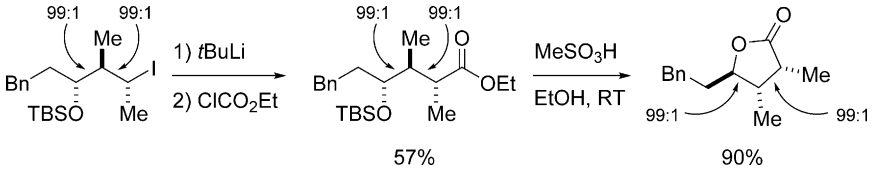

Lithium is the star: An I–Li-exchange allows a highly stereoretentive preparation of a range of α-chiral secondary alkyllithium reagents, which, after quenching with $ClCO_2Et$, provide both *anti*- and *syn*-ester carboxylates bearing two or three adjacent stereocenters.

Lithium Reagents

*V. Morozova, K. Moriya, P. Mayer, P. Knochel**

■■ – ■■

Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters