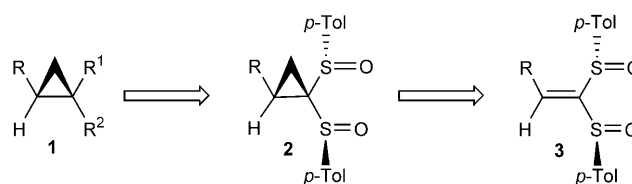


Convergent Preparation of Enantiomerically Pure Polyalkylated Cyclopropane Derivatives**

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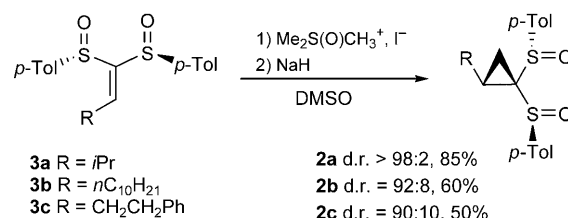
Cyclopropane is a basic structural element in a wide range of naturally occurring compounds,^[1] and has been used as a versatile intermediate in the synthesis of more functionalized cyclic^[2] and acyclic alkanes.^[3] In the last few decades, most of the synthetic efforts have focused on the enantioselective synthesis of cyclopropanes,^[4] however, new and more efficient methods for the preparation of these entities in enantiomerically enriched form are still evolving.^[5] These methods can be divided into four types: the halomethylmetal-mediated cyclopropanation reaction,^[6–8] the transition-metal-catalyzed decomposition of diazo compounds,^[6] the nucleophilic addition/ring closure sequence, and the hydro- and carbometallation reaction of strained cyclopropene derivatives.^[5a] All of these methods are among the most powerful and innovative approaches, but they usually lead to functionalized cyclopropanes. To prepare nonfunctionalized, enantiomerically enriched disubstituted cyclopropanes (95% *ee*), we successfully reported the (–)-sparteine-catalyzed enantioselective carbolithiation^[9] of styrenyl derivatives which then undergo a 1,3-elimination reaction.^[10] These reactions were restricted to aryl- and vinyl-substituted^[10] cyclopropanes. To develop an even more general approach to the preparation of enantiomerically pure polyalkylated cyclopropanes (**1**; R, R¹, R² = alkyl groups), we envisaged subjecting **2** to a combination of two consecutive selective sulfoxide/lithium exchanges,^[12] a transmetalation reaction, and then a reaction with an electrophile (Scheme 1). The sulfoxide/lithium exchange occurs when the reactive organometallic reagent reacts at the sulfur center of the sulfoxide, through an S_N2 process, to generate a more stable organometallic leaving group.^[12f] Alkylidene bis(*p*-tolylsulfoxides)^[12] (**3**) were recently used as highly versatile partners for asymmetric syntheses^[13] in the



Scheme 1. Retrosynthetic analysis for the preparation of enantiomerically pure polysubstituted cyclopropanes (**1**).

context of radical chemistry,^[14] polar Michael additions,^[15] and the Michael-initiated ring closure reaction which is used herein as the key step for the preparation of cyclopropane **2**.^[16]

Indeed, when the sulfur ylide, generated in situ by deprotonation of trimethyloxosulfonium iodide with NaH in DMSO, was reacted with alkylidene bis(*p*-tolylsulfoxides) **3a–c** and corresponding bis(*p*-tolylsulfinyl)cyclopropanes **2a–c** were obtained in good to excellent diastereoisomeric ratios (Scheme 2). Each of the products **2b** and **2c** were easily separated by column chromatography on silica gel to obtain each diastereoisomer as a pure isomer. The absolute configuration of **2a** was determined by X-ray crystallographic analysis (see the Supporting Information) and by using the already established model.^[16]



Scheme 2. Diastereoselective cyclopropanation reaction of alkylidene bis(*p*-tolylsulfoxides) (**3**).

When **2a** (R = *i*Pr) was treated at low temperature with *n*BuLi, a selective sulfoxide/lithium exchange took place to give the expected cyclopropyllithium species **5a**, which after methanolysis, afforded cyclopropane **6a** in excellent yield as a single diastereoisomer (Table 1, entry 1). An excess of *n*BuLi (routinely 3 equiv) was used for the exchange reaction to react with the *n*butyl-*p*-tolylsulfoxide formed in situ, thus avoiding protonation of **5a** by the acidic hydrogen atoms α to the sulfinyl group of the *n*butyl-*p*-tolylsulfoxide.^[17]

The stereochemistry of the sulfoxide/lithium exchange was determined either by ¹H NMR spectroscopy (the coupling constant of the two cyclopropyl hydrogen atoms of **6b**,

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Table 1: Preparation of diastereoselectively pure cyclopropylsulfoxide derivatives **6a–j**

Entry ^[a]	Substrate, R	R ¹ X	R ¹	d.r. ^[b]	Yield [%] ^[c]
1	2a , <i>i</i> Pr	MeOH	H	> 98:2 (6a)	80
2	2b , <i>n</i> C ₁₀ H ₂₁	MeOH	H	> 98:2 (6b)	70
3	2a , <i>i</i> Pr	CH ₃ I	CH ₃	> 98:2 (6c)	70
4	2a , <i>i</i> Pr	PhCH ₂ Br	PhCH ₂	> 98:2 (6d)	60
5	2a , <i>i</i> Pr	CH ₂ CHCH ₂ Br	CH ₂ CHCH ₂	> 98:2 (6e)	60
6	2a , <i>i</i> Pr	<i>n</i> BuI	<i>n</i> Bu	> 98:2 (6f)	65
7	2b , <i>n</i> C ₁₀ H ₂₁	CH ₃ I	CH ₃	> 98:2 (6g)	65
8	2b , <i>n</i> C ₁₀ H ₂₁	<i>n</i> BuI	<i>n</i> Bu	> 98:2 (6h)	65
9	2c , PhCH ₂ CH ₂	CH ₃ I	CH ₃	> 98:2 (6i)	60
10	2b , <i>n</i> C ₁₀ H ₂₁	CH ₂ OH	CH ₂ OH	> 98:2 (6j)	70

[a] See experimental section. [b] Determined from the crude reaction mixture by using ¹H NMR spectroscopy; only one diastereoisomer was detected. [c] Yield of product isolated after purification by column chromatography.

$J = 4.5$ Hz, corresponds to a *trans* relationship) or by X-ray crystallographic analysis of sulfone **7b** (see the Supporting Information), which is obtained after oxidation of the sulfinyl group. Our mechanistic hypothesis is based on the more hindered *syn*-selective sulfoxide/lithium exchange as it results in the release of strain. This assumption was corroborated by obtaining a 1:1 mixture of diastereoisomers when the more sterically demanding *t*BuLi was used, instead of *n*BuLi, for the sulfoxide/lithium exchange. If the lithiation initially occurred *trans* to the cyclopropane substituent, then subsequent alkylation would occur with inversion of configuration; to rule out the possibility, we compared the stereochemical outcome of the reactions run with H₂O and CH₃I. Indeed, the stereochemical outcome for the reaction of the classical sp³ carbon center with an appended α-lithiosulfoxide group may be dependent on the electrophile; electrophiles containing oxygen atoms (H₂O, D₂O, and CH₂O) react with such sp³ centers in THF with retention of configuration whereas CH₃I reacts with inversion.^[18] In the case of cyclopropyl lithiosulfoxide **5**, MeOH and CH₃I react with retention of configuration (Table 1, entries 2 and 3; **6b** and **6c** have the same stereochemistry as determined by X-ray crystallographic analyses). The stereochemistry of other reac-

tion products was assigned by analogy. Various electrophiles could be added to the reaction mixture and in all cases the disubstituted cyclopropyl sulfoxides were obtained as a single diastereoisomer (Table 1, entries 3–10). The next step, namely the second sulfoxide/lithium exchange was then investigated (Table 2). The sulfoxide/metal exchange is known to proceed with retention of configuration at the carbon center,^[19] and since the lithiated cyclopropyl species are configurationally stable^[20] the diastereoisomerically pure cyclopropyl sulfoxides (**6**) were transformed into the corresponding *cis*-lithiated cyclopropyl species (**8**) and then into enantiomerically pure products (*cis*-**9a–c**) after hydrolysis. Indeed, this stereochemical outcome was verified when cyclopropyl sulfoxide **6d** was treated with *n*BuLi (2 equiv) at –80 °C in THF and **6h** was treated with *t*BuLi (1 equiv) at –80 °C in THF (Table 2, entries 1 and 3). Similar results were obtained when **6g** was treated with *i*PrMgCl at room temperature in THF (Table 2, entry 2) or with *t*BuLi (1 equiv) at –80 °C in toluene (Table 2, entry 4). In all cases, the reaction proceeded smoothly and led to the expected *cis*-dialkylated cyclopropanes **9a–e** after hydrolysis; the products were isolated in good yields as a single isomer.

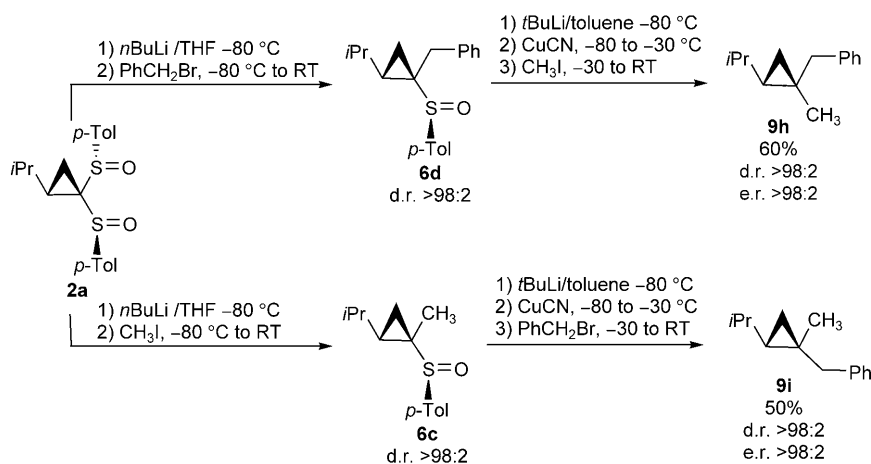
As expected, when the exchange was run in THF, the resulting basic tertiary organometallic species **8** rapidly reacted by deprotonating the solvent; therefore, conditions for additional alkylation reactions of **8** were found to work best in a nonbasic solvent such as toluene (Table 2, entry 4). In this case, the addition of MeOD led to the corresponding deuteriocyclopropane **9d** in 80 % yield as single isomer. In addition, when **6j** was subjected to the sulfoxide/lithium exchange and subsequent hydrolysis, the corresponding (2-decylcyclopropyl)methanol^[21] **9e** was isolated in greater than 97 % *ee* (Table 2, entry 5, determined after correlation with an authentic sample).

Table 2: Preparation of Enantiomerically enriched 1,2-di- and 1,2,2'-trisubstituted cyclopropane derivatives **9a–i**

Entry	Substrate, R	R ¹	Reagent	R ²	d.r. ^[f]	Yield [%] ^[g]
1 ^[a]	6d , <i>i</i> Pr	PhCH ₂	H ₂ O	H	> 98:2 (9a)	70
2 ^[b]	6g , <i>n</i> C ₁₀ H ₂₁	CH ₃	H ₂ O	H	> 98:2 (9b)	80
3 ^[c]	6h , <i>n</i> C ₁₀ H ₂₁	<i>n</i> Bu	H ₂ O	H	> 98:2 (9c)	82
4 ^[d]	6g , <i>n</i> C ₁₀ H ₂₁	CH ₃	CH ₃ OD	D	> 98:2 (9d)	80
5 ^[d]	6j , <i>n</i> C ₁₀ H ₂₁	CH ₂ OH	H ₂ O	H	> 98:2 (9e)	50
6 ^[d]	6g , <i>n</i> C ₁₀ H ₂₁	CH ₃	<i>n</i> PrCHO	CH(OH)Pr ^[h]	> 98:2 (9f)	60
7 ^[d]	6i , PhCH ₂ CH ₂	CH ₃	<i>p</i> -TolylSO ₃ - <i>p</i> -Tolyl	<i>S</i> -Tol	> 98:2 (9g)	82
8 ^[e]	6d , <i>i</i> Pr	PhCH ₂	CH ₃ I	CH ₃	> 98:2 (9h)	60
9 ^[e]	6c , <i>i</i> Pr	CH ₃	PhCH ₂ Br	PhCH ₂	> 98:2 (9i)	50

[a] *n*BuLi in THF was used for the exchange. [b] *i*PrMgCl in THF at RT was used for the exchange. [c] *t*BuLi in THF was used for the exchange. [d] *t*BuLi in toluene was used for the exchange. [e] After the exchange, a Li to copper transmetalation with CuCN was performed for the alkylation reaction. [f] Determined on the crude reaction mixture by ¹H NMR spectroscopy. [g] Yield of isolated product after purification by column chromatography. [h] A 1:1 mixture of isomers is formed; isomeric at the carbinol center.

Stereo- and enantiomerically pure cyclopropyl lithium species **8** could also react with several electrophiles, such as an aldehyde (Table 2, entry 6) or *S*-*p*-tolyl-4-methylbenzenethio-sulfonate (Table 2, entry 7). However, when less reactive electrophiles were used, such as alkyl halides, tertiary cyclopropyl lithium species **8** was not nucleophilic enough in toluene (addition of THF would lead to a protonation of the tertiary alkyl lithium species as previously stated),^[22] necessitating a transmetalation to the organocopper species. The transmetalation of a cyclopropyl metal species to the cyclopropyl copper species occurs with retention of configuration,^[23] and cyclopropyl copper species are configurationally stable;^[24] thus subjecting **6d** and **c** to modified conditions including transmetalation and subsequent addition of alkyl halides as electrophiles (Table 2, entries 8 and 9) led to alkylated cyclopropane derivatives **9h** and **9i** respectively with retention configuration. This methodology leads to the preparation of the two diastereo- and enantiomerically pure trisubstituted cyclopropyl derivatives from the same precursor. As shown in Scheme 3, permutation of the electrophiles introduced after each of the two sulfoxide/lithium exchange reactions allows the formation of the two diastereoisomers (**9h** and **i**), which have different absolute configurations at the quaternary centers.



Scheme 3. Independent preparation of the two diastereo- and enantiomerically pure cyclopropanes.

In conclusion, selective sulfoxide/lithium exchange reactions lead to the unique preparation of diastereo- and enantiomerically pure polyalkylated cyclopropanes. This new reaction allows the independent formation of both diastereoisomers from a common starting material. Additional studies are now ongoing in our research group to extend this methodology to more functionalized substrates.

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