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# Elucidation of the Reaction Mechanism of *ortho→α* Transmetalation Reactions of Alkyl Aryl Sulfone Carbanions

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The sulfonyl group, as an electron-accepting function, displays a strong acidifying effect on neighboring  $\alpha$ -hydrogen atoms, leading to their deprotonation by bases. Recently, reversal of the metalation selectivity of  $\alpha$ , $\gamma$ -branched alkyl aryl sulfones was described, which instead undergo directed *ortho*-metalation with good regioselectivity, despite having a more acidic  $\alpha$ -proton. Upon warming, a transmetalation to the  $\alpha$ -carbanion proceeds; however, nothing is known about the course of this transmetalation. Here, a mechanistic study is presented that sheds light on the facility of the initial metalation and the subsequent transmetalation. Large kinetic isotope effects were observed for both the initial deprotonation and the *ortho*— $\alpha$  transmetalation, which strongly influence the initial metalation selectivity. The results of a kinetic investigation of the transmetalation and a crossover study indicate that a concerted intermolecular pathway, either from an aggregate or from a monomeric aryllithium, prevails. The potential involvement of a stepwise process via *ortho*, $\alpha$ -dilithium intermediates was investigated, but no hint of their involvement was found.

#### Introduction

Carbanions are widely used intermediates in organic chemistry.<sup>[1]</sup> Their generation is especially facile when electron-accepting activating groups are present in the vicinity of the envisaged site. Normally, the regioselectivity of the deprotonation process can be easily predicted. If an alkyl group has hydrogen atoms in an  $\alpha$ -position to the electron-accepting group, deprotonation takes place at this position because of its much lower p $K_a$  value. If not, the activating group can still act as a Lewis base, coordinating the counterion of the base, especially for organolithium bases, and direct the deprotonation in a more distant position according to the complex-induced proximity effect (CIPE).<sup>[2]</sup> The most common class of these processes constitute directed *ortho*-metalations (DoM) at aryl units. Normally these two basic metalation modes exclude each other.

The sulfone group is a commonly applied activating group for the generation of carbanions and usually acts according to the rules outlined above.<sup>[3]</sup> However, we recently found a surprising reversal of the lithiation selectivity of  $\alpha$ , $\gamma$ -branched alkyl aryl sulfones **I**.<sup>[4]</sup> in which selective DoM at the aryl unit prevails, despite the presence of a considerably more acidic  $\alpha$ -proton (Scheme 1). The resulting aryl-lithium intermediates **II** are stable at low temperature and can react with a number of electrophiles, but they undergo

transmetalation to the thermodynamically more stable  $\alpha$ sulfonyl carbanions III above -40 °C. The degree of branching determined the metalation selectivity as well as the onset of the transmetalation from II to III. In contrast,  $\alpha$ -branched sulfones lacking the additional  $\gamma$ -branching deprotonated as usual in the  $\alpha$ -position, leading directly to III. The Gais group found a similar DoM/transmetalation behavior for conformationally constrained sulfoximines.<sup>[5]</sup>



Scheme 1. Metalation selectivity dependence of sulfones I on the substitution pattern.

Nothing is known about the mechanism of this transmetalation, but this is critical for the synthetic applicability of **II** or **III**. Three pathways can be envisaged to account for the transmetalation of branched aryllithiums **V** resulting from sulfone **IV** to  $\alpha$ -sulfonylalkyllithium **IX** (Scheme 2). It may proceed in an intramolecular manner through a concerted process via a four-membered transition state **VI**. Alternatively, two intermolecular pathways may be followed. On one hand, a concerted proton transfer from an aggregate<sup>[6]</sup> or two monomeric *ortho*-sulfonylphenyllithium units **V** via a symmetrical transition state such as **VII** may occur.

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 $\dot{R}^2$ 

Scheme 2. Potential course of the transmetalation reaction of *ortho*-sulfonylphenyllithium V to  $\alpha$ -sulfonylalkyllithium IX.

On the other hand, two consecutive proton transfers may first lead to an *ortho*, $\alpha$ -dilithium intermediate **VIII** and substrate **IV** as the rate-limiting step, from which a second, potentially fast proton transfer follows, leading to two units of **IX**. Indeed, intermediates **VIII** were previously individually generated by Gais and colleagues by a reverse strategy of initial  $\alpha$ - and subsequent *ortho*-metalation.<sup>[5,7]</sup>

To gain insight into reaction mechanisms, kinetic investigations are often undertaken. Such investigations can distinguish between unimolecular vs. bimolecular pathways, which is a situation given here with VI vs. VII and VIII/IV, however not the latter two, because the same rate law may apply to both. Another convenient strategy to determine whether a reaction proceeds in an intra- or intermolecular manner is crossover experiments. It can be hypothesized that differentially deuterated precursors would be ideal reaction partners for the given case, because it can be expected that the reaction rates are different, but the general course should not change. Moreover, the products can be directly and conveniently detected and identified by NMR and mass spectrometry techniques. This necessitates the determination of deuterium kinetic isotope effects (KIE).<sup>[8]</sup> Especially during metalation reactions, large deuterium KIEs may be observed, which influence their rate and selectivity.<sup>[9]</sup>

We provide here a mechanistic study of the transmetalation of *ortho*-sulfonylphenyllithium intermediates V to the corresponding  $\alpha$ -sulfonylalkyllithium compounds IX. Results of a kinetic investigation for the transmetalation reaction, studies aimed at the determination of deuterium KIEs, crossover experiments, and a study to determine whether dilithium intermediates VIII are competent intermediates, are presented. Based on these results a plausible mechanistic course of the transmetalation is suggested.

#### Results

#### **Preparation of Starting Materials**

2,6-Dimethylhept-4-yl phenyl sulfone (2) and pent-3-yl phenyl sulfone (3) were prepared from commercially available methyl phenyl sulfone (1a) by deprotonation with *n*BuLi in the presence of TMEDA and subsequent alkylation with isobutyl or ethyl iodide, respectively (Scheme 3).<sup>[4b]</sup> The *para*-methyl-substituted sulfone 4 was similarly prepared from 4-(methylsulfonyl)toluene (1b) by deprotonation with *n*BuLi and alkylation with isobutyl iodide.



Scheme 3. Preparation of  $\alpha$ -branched aryl sulfones 2–4.

The deuterated sulfones intended for use in the determination of KIEs and crossover experiments were prepared by deprotonation of **2–4** and subsequent deuteration (Scheme 4). *ortho,ortho'*-Dideuterated compound  $o,o-D_2-2$ was synthesized from sulfone **2** via *ortho*-deuterated *o*-D-**2** by two consecutive deprotonations with *n*BuLi and subsequent addition of deuterium oxide; the product was formed

in 98% yield as a 92:8 mixture of  $o,o-D_2-2$  and monodeuterated derivative o-D-2. It was, however, not possible to deuterate both positions in 100% yield without further deuteration in the  $\alpha$ -position. Deprotonation of  $o,o-D_2-2$  under similar conditions with a slight excess of BuLi at -20 °C and addition of  $D_2O$  gave the trideuterated sulfone  $o,o,a-D_3-2$  in very good yield and complete deuteration.  $\alpha$ -Deuterated sulfones  $\alpha$ -D-3 and  $\alpha$ -D-4 were obtained by deprotonation/deuteration of 3 and 4, respectively, with complete deuteration.



Scheme 4. Preparation of deuterated alkyl aryl sulfones.

## Mechanistic Investigations on the Course of the Transmetalation

#### **Kinetics**

Compound 2 served as the substrate for determination of the kinetics of the transmetalation. It was deprotonated by *n*BuLi in tetrahydrofuran (THF) in the presence of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) at -50, -45, -40, -35, and -30 °C (Figure 1, Supporting Information Tables S3–7). The use of TMEDA proved to be beneficial for obtaining optimal *o*-/*a*-selectivity.<sup>[4]</sup> After given times, aliquots were taken, the reaction was quenched by the addition of D<sub>2</sub>O, and the sample was analyzed by <sup>1</sup>H NMR and its mass balance was recorded, which proved to be quantitative. The ratio of deuterated compounds *o*-D-2



Figure 1. Kinetic trace of the transmetalation of o-Li-2 to  $\alpha$ -Li-2 (for the raw data see the Supporting Information, Tables S3–7).

and  $\alpha$ -D-2 reflects the ratio of organolithium intermediates *o*-Li-2 and  $\alpha$ -Li-2.



time (s)

Figure 2. First-order plot for the transmetalation of monomeric ortho-sulfonylphenyllithium o-Li-2 to a-Li-2.

The obtained values fit best to first-order kinetics (Figure 2). The first-order rate constants of the transmetalation were calculated to  $k = 2.67 \times 10^{-4} \text{ s}^{-1}$  at -50 °C, k = $3.85 \times 10^{-4} \text{ s}^{-1}$  at -45 °C,  $k = 4.85 \times 10^{-4} \text{ s}^{-1}$  at -40 °C, k = $1.02 \times 10^{-3} \text{ s}^{-1}$  at -35 °C, and  $k = 2.28 \times 10^{-3} \text{ s}^{-1}$  at -30 °C. An attempt to apply second-order kinetics resulted in a more significant deviation from linearity (Figure S1). The integral method for determining the reaction order was also used,<sup>[10]</sup> however, the calculated values of the rate constants differed considerably. Because the sulfonyllithium intermediates o-Li-2 or a-Li-2 may occur aggregated in solution,<sup>[1g,6,7e,11]</sup> the kinetics were also calculated for dimers or tetramers of these intermediates, however, more satisfactory results were not obtained. These results suggest that the transmetalation may proceed either in an intramolecular manner via VI or as an aggregate via a transition state such as VII (cf. Scheme 2).

To gain further insight into the reaction, the kinetics of the transmetalation of o-Li-2 to  $\alpha$ -Li-2 were determined at -40 °C, at three different concentrations (Figure 3, Supporting Information, Table S8). The results clearly showed that the rate of the transmetalation increased with increasing concentration, which contradicts first-order kinetics, but is more in line with second-order kinetics.



Figure 3. Dependence of the transmetalation rate on the concentration at -40 °C. The trace at c = 0.083 mol/L was taken from the kinetic trace in Figure 1.

#### Kinetic Isotope Effects

We intended to use differentially deuterated sulfones in a crossover study (see below). However, it first had to be confirmed that deuterium KIEs operate with sufficiently high values to avoid undesired *ortho* $\rightarrow \alpha$  deuterium transfer and competitive dedeuteration by the base. Whereas KIEs for DoM show typical values exceeding 19,<sup>[9e–9g]</sup> KIEs for sulfones have so far not been determined. Therefore, metalation and transmetalation studies with differentially deuterated sulfones were performed.

The intramolecular kinetic isotope effect for the *ortho*-lithiation of sulfone *o*-D-2 with 96% *ortho*-D was deter-

mined by treatment with 0.9 equiv. of *n*BuLi in the presence of TMEDA at -78 °C for 5 min (Scheme 5). Two samples were taken at the same time and separately quenched with water and D<sub>2</sub>O, respectively, and analyzed by <sup>1</sup>H NMR spectroscopy. The intramolecular KIE was derived from the isotopic ratio of products *o*-D-2 and 2 after quenching with water, as indicated by the increased integral of the *ortho*-H resonance, which amounted to a maximum of 2%. The aliquot of the reaction quenched by D<sub>2</sub>O revealed that lithiation proceeded to an extent of 84%. This leads to a *ortho*-D/H ratio of 82:2, from which an intramolecular KIE of  $k_{\rm H}/k_{\rm D} = 41$  for the *ortho*-lithiation of *o*-D-2 can be derived. However, the error must be considered relatively large because of the small extent of *ortho*-H incorporation<sup>[9f]</sup> and the inherent integration error of <sup>1</sup>H NMR spectroscopy.



Scheme 5. Determination of the intramolecular KIE for *ortho*-lithiation of *o*-D-2.

In trideuterated sulfone  $o, o, \alpha$ -D<sub>3</sub>-2, the ortho $\rightarrow \alpha$  dedeuteration selectivity should be similar to that in 2, thus the facility of the subsequent *ortho* $\rightarrow \alpha$  transmetalation may be derived. When  $o_1, o_2, \alpha$ -D<sub>3</sub>-2 was lithiated under standard conditions and quenched with water at -78 °C, a mixture of o,α-D<sub>2</sub>-2 and o,o-D<sub>2</sub>-2 was obtained in a 90:9 ratio (Table 1, entry 1). The *ortho*-metalation selectivity of  $o_1, o_2, \alpha$ -D<sub>3</sub>-2 was thus slightly lower than that of 2, which amounted to a ratio of 31:1 under identical conditions.<sup>[4b]</sup> The ortho $\rightarrow \alpha$ transmetalation did not take place at temperatures below -40 °C, as indicated by the almost constant hydrogen content in *ortho-* and  $\alpha$ -positions of  $o,\alpha$ -D<sub>2</sub>-2 and o,o-D<sub>2</sub>-2, respectively (entries 2 and 3). The transmetalation started to proceed at temperatures of -40 to 0 °C (entries 4 and 5), thus at significantly higher temperature compared with that of 2 (-50 °C, see above).<sup>[4b]</sup> Therefore an exact kinetic iso-

Table 1. DoM-transmetalation of trideuterated sulfone o,o, $\alpha$ -D<sub>3</sub>-2.

| D<br>0,0,<br>100 | $\begin{array}{c} O_2 \\ S \\ D \\ D \\ \rho \\ \rho$ | $p_{D}^{\text{ILi}}$ , $D$ $C$<br>EDA, $T$ | $\frac{1}{2} \frac{i \Pr }{D} \frac{D}{i \Pr} \frac{D}{D^2} \frac{i \Pr}{i \Pr}$ $\frac{1}{i \Pr} \frac{D}{i \Pr} \frac{D}{D} \frac{i \Pr}{i \Pr}$ $-2  0, 0 - D_2 - 2$ |
|------------------|---|--|---|
| Entry            | <i>T</i> [°C]   | t [min] <sup>[a]</sup>   | <i>o</i> ,α-D <sub>2</sub> - <b>2</b> / <i>o</i> , <i>o</i> -D <sub>2</sub> - <b>2</b> [%] <sup>[b]</sup>   |
| [                | -78   | 10   | 90:9 <sup>[c]</sup>   |
| 2                | -60   | 20   | 92:8 <sup>[c]</sup>   |
| 3                | -40   | 30   | 93:7  |
| 1                | -20   | 40   | 87:12   |
| 5                | 0   | 50   | 30:63   |
|                  |   |  |   |

[a] Time refers to the start of the deprotonation. [b] Determined by <sup>1</sup>H NMR spectroscopy. [c] Reaction run in duplicate with similar results.

tope effect for the *ortho* $\rightarrow \alpha$  transmetalation could not be determined, but it must be large.

ortho, ortho'-Dideuterated sulfone o, o-D2-2 (o, o-D2-2/o-D-2 92:8 mixture based on 185% ortho-D, 15% residual ortho-H by integration of the <sup>1</sup>H NMR spectrum) was used to study the regioselectivity of the metalation (Table 2). Two parallel metalation experiments were performed with the o,o-D<sub>2</sub>-2/o-D-2 mixture under the standard conditions at -78 °C. One of the setups was subsequently guenched with  $D_2O$  at given temperatures and times to determine the metalation regioselectivity to o-D,o-Li-2 and/or o,o-D<sub>2</sub>,a-Li-2 and the second with water to assess whether DoM to o-D,o-Li-2 proceeded at all. Quenching the organolithium intermediates at -78 °C after 1 min or 5 min metalation time with D<sub>2</sub>O and analyzing the mixture by <sup>1</sup>H NMR spectroscopy led to an essentially unchanged ortho-proton integral of 15%, corresponding to 185% D compared to the starting mixture; however, the initially 100% integral of the  $\alpha$ -proton decreased to 46 and 50%, respectively. This indicates the formation of an almost 1:1 mixture consisting of recovered o,o-D2-2 on one hand and the sum of trideuterated product  $o,o,\alpha$ -D<sub>3</sub>-2 (major) and  $o,\alpha$ -D<sub>2</sub>-2 (minor) on the other hand (entries 1 and 2). Trideuterated  $o,o,\alpha$ -D<sub>3</sub>-2 thus results from competitive initial  $\alpha$ -deprotonation of o,o-D<sub>2</sub>-2 to o,o-D<sub>2</sub>, $\alpha$ -Li-2 at -78 °C and subsequent deuteration. Minor amounts of dideuterated  $o,\alpha$ -D<sub>2</sub>-2 must also be generated by  $\alpha$ -deprotonation, because the transmetalation of o-D,o-Li-2 to o-D, $\alpha$ -Li-2 should not operate at this temperature, as in the case of o-Li-2 to  $\alpha$ -Li-2.<sup>[4b]</sup>

Warming the reaction mixture to -20 °C during 15 min and quenching with D<sub>2</sub>O revealed a sharp increase of the *ortho*-proton integral to 59%, corresponding to a decreased deuterium content of 141% at the *ortho*-position and an almost equal decrease of the proton integral at the  $\alpha$ -position to 10% (= 90% deuteration) (entry 3). Thus, the transmetalation of *o*-D,*o*-Li-2 to *o*-D, $\alpha$ -Li-2 took place on warming, similar to that of *o*-Li-2 to  $\alpha$ -Li-2 in the nondeuterated series (see above).<sup>[4b]</sup>

The setup quenched with water at -78 °C after 1 min or 5 min confirmed that metalation of the *o*,*o*-D<sub>2</sub>-2/*o*-D-2 mixture was complete and it complements the deuteration result. The *ortho*-proton content is expected to be 100% if

Table 2. Metalation selectivity and transmetalation of dideuterated sulfone o,o-D<sub>2</sub>-2.<sup>[a]</sup>



| Quench by: |               |                        | D <sub>2</sub> O |   | H <sub>2</sub> O  |   |
|------------|---------------|------------------------|------------------|---|---|---|
| Entry      | <i>T</i> [°C] | t [min] <sup>[b]</sup> |                  | $\% \alpha$ -D<br>( $o, o, \alpha$ -D <sub>3</sub> -2 + $o, \alpha$ -D <sub>2</sub> -2) | $\% ortho-H^{[d]}$<br>( <i>o</i> , <i>o</i> -D <sub>2</sub> -2 + <i>o</i> -D-2) | % α-H<br>( <i>o</i> , <i>o</i> -D <sub>2</sub> - <b>2</b> + <i>o</i> -D- <b>2</b> ) |
| 1          | -78           | 1                      | 185              | 46  | 63  | 97  |
| 2          | -78           | 5                      | 188              | 50  | 69  | 96  |
| 3          | -20           | 15                     | 141              | 90  | 64  | 93  |

[a] Reaction run in duplicate with very similar results. [b] Time refers to the start of the deprotonation. [c] Percent deuterium in the *ortho*-position determined by integration of the residual *ortho*-H in the <sup>1</sup>H NMR spectrum. Theoretically, *o*,*o*-D<sub>2</sub>-2 has two *ortho*-D = 200%. [d] Percent *ortho*-H by integration of the <sup>1</sup>H NMR spectrum; 100% = one *ortho*-H. The higher percentage of the *ortho*-hydrogen resonance than expected is predominately because of the presence of monodeuterated *o*-D-2 in the starting material.

exclusive ortho-metalation of o,o-D<sub>2</sub>-2 followed by protonation occurred; the experimentally found ortho-proton content of 63 and 69%, respectively, indicated that a little more than 50% of ortho-metalation to o-D,o-Li-2 occurred (entries 1 and 2). The observed higher value of 63% protons is accounted for by the presence of o-D-2 in the starting material o,o-D<sub>2</sub>-2, the ortho-proton content of which must be added. No change was observed on warming, because the transmetalation to o-D, $\alpha$ -Li-2 proceeds with exchange of the  $\alpha$ -hydrogen atom of o-D,o-Li-2 (entry 3). The proton content in the  $\alpha$ -position remained, as expected, close to 100%, indicating that no transmetalation with exchange of a deuterium atom occurred. These results showed that dedeuteration at the ortho-position of o,o-D<sub>2</sub>-2 leading to o-D,o-Li-2 was significantly retarded compared with that of **2**, so that direct deprotonation at the  $\alpha$ -position leading to  $o_1o_2,\alpha$ -Li-2 competed with a similar rate instead.

Another potential crossover candidate was deuterated 3pentylsulfone  $\alpha$ -D-3. It may be expected that this substrate returns unchanged  $\alpha$ -D-3 after the normally observed metalation to  $\alpha$ -Li-3 and subsequent reaction with D<sub>2</sub>O, but gives 3 by quenching with water, provided that no significant isotope effect operates. In the event, lithiation of  $\alpha$ -D-3 at -78 °C and quenching with D<sub>2</sub>O gave in contrast *ortho*,  $\alpha$ dideuterated derivative  $o,\alpha$ -D<sub>2</sub>-3 together with  $\alpha$ -D-3 in a ratio of 3:7, which did not change significantly over 10 min at -78 °C (Table 3, entries 1-3). Protonation provided α-D-3 and 3 in a 3:7 ratio. This clearly shows that dedeuteration of  $\alpha$ -D-3 at the  $\alpha$ -position, generating  $\alpha$ -Li-3, was retarded compared with the  $\alpha$ -deprotonation of  $3^{[4b]}$  to such an extent that DoM resulting in the formation of α-D,o-Li-3

Table 3. Metalation selectivity of  $\alpha$ -deuterated sulfone  $\alpha$ -D-3.



[a] Time refers to the start of the deprotonation. [b] Determined by <sup>1</sup>H NMR spectroscopy.

competed to a significant extent. The  $\alpha$ -D,o-Li-3/ $\alpha$ -Li-3 ratio of 3:7 did not change at -78 °C during 10 min, indicating that the ortho $\rightarrow \alpha$  transmetalation of  $\alpha$ -D,o-Li-3 to o-D, $\alpha$ -Li-3 does not take place at this temperature.

and a-D-3 provided valuable information about the metalation selectivity, which changes significantly when hydrogen atoms in the *ortho*- as well as in the  $\alpha$ -position are substituted by deuterium. Although some kinetic isotope effects could not be quantified due to the switch of metalation selectivity, they can be considered large at a qualitative level. These facts did not allow the application of  $o,o-D_2-2$ ,  $o,o,\alpha-D_3-2$ , and  $\alpha$ -D-3 in crossover experiments, because their rates of metalation and/or transmetalation are not compatible with those of 2.

The *ortho* $\rightarrow \alpha$  transmetalation also has a large kinetic isotope effect, which retards it significantly, based on the transmetalation result of  $o_1, o_2, \alpha$ -D<sub>3</sub>-2. This bodes well for the application of an  $\alpha$ -deuterated substrate in the crossover study, which is very similar to 2, but bears a remote substituent at the aromatic ring. Therefore, the metalation/transmetalation behavior of *p*-tolyl sulfone **4** was studied under identical conditions to those for sulfone 2 (Table 4). The initially formed *ortho*-sulfonylphenyllithium *o*-Li-4 transmetallated to  $\alpha$ -Li-4, as indicated by isolation of the deuterated compounds o-D-4 and/or  $\alpha$ -D-4, but slightly slower than observed for 2.<sup>[4b]</sup>

Table 4. Deprotonation and transmetalation of *p*-tolyl sulfone 4.



[a] Time after start of the deprotonation.

Based on these results,  $\alpha$ -deuterated *p*-tolyl sulfone  $\alpha$ -D-4 can indeed serve as one of the components in the crossover reaction because it has ortho-hydrogen atoms that are distinct from those of 2 (Scheme 6). However, its metalation and transmetalation behavior had to be studied individually. DoM of  $\alpha$ -D-4 under standard conditions, warming to

1

0 °C over 50 min and quenching with D<sub>2</sub>O furnished *or*tho,α-dideuterated sulfone  $o,\alpha$ -D<sub>2</sub>-4 as the exclusive product in 92% yield, thus confirming DoM. However, it did not prove that undesirable transmetalation was not interfering to some extent. Therefore, the mixture was quenched in parallel with water at -20 °C after 30 min, which provided 95%  $\alpha$ -D-4 and maximally 5% *ortho*-deuterated product *o*-D-4, as determined by integration of the <sup>1</sup>H NMR spectra. These results clearly show that deprotonation of  $\alpha$ -D-4 and subsequent deuteration or protonation took place in the *ortho*-position and that the *ortho*- $\alpha$  transmetalation indeed proceeded only to a very small extent, which can be explained by the significant kinetic isotope effect of the transmetalation (cf. Table 1). These features allow application of  $\alpha$ -D-4 in the crossover study.



Scheme 6. Time- and temperature-dependent metalation of  $\alpha$ -D-4 followed by deuteration or protonation.

#### Interfering Proton Transfer Equilibria between ortho-Lithiated Sulfones and their Neutral Precursors

An important factor that may contribute to the transmetalation process is the ability of neutral protonated sulfones to serve as proton donors toward the ortho-sulfonylphenyllithium intermediates o-Li-2, for which the  $\alpha$ -proton with  $pK_a$  values of 29–31 [dimethyl sulfoxide (DMSO)] should be sufficiently acidic.<sup>[12]</sup> Unhindered compounds 3 and  $\alpha$ -D-3 indeed proved to be proton (deuterium) donors towards the ortho-sulfonylphenyllithium intermediate o-Li-2 (see the Supporting Information, Tables S1 and S2). Thus, complete deprotonation must be ensured with unhindered sulfones to obtain mechanistically meaningful results. This is, however, not true when neutral branched sulfones are applied as proton source. When sulfone 2 was deprotonated using only 0.5 equiv. *n*BuLi in the presence of TMEDA (cf. Figure 1), the degree of deprotonation to *o*-Li-2 was clearly only 50%, and the remainder of 2 could, in principle, serve as a proton donor from the  $\alpha$ -position and thus mediate the transmetalation. This is, however, not the case (Table 5). The ortho-sulfonylphenyllithium o-Li-2 remains stable at -78 to -60 °C (entries 1 and 2) and transmetallated essentially in an identical manner to that observed under the previously reported stoichiometric lithiation and deuteration conditions (entries 3–5).<sup>[4b]</sup> Thus 2, and probably also related sulfone 4, are unreactive as proton donors toward o-Li-2 at low temperature and, thus, even though lithiation

of **2** is not complete, remaining **2** will not mediate the transmetalation.

Table 5. Deprotonation of sulfone 2 by 0.5 equiv. *n*BuLi and its transmetalation.

| Entry | <i>T</i> [°C] | t [min] <sup>[a]</sup> | <i>o</i> -D-2/α-D-2 | <i>o</i> -D-2/α-D-2 <sup>[b]</sup> |
|-------|---------------|------------------------|---------------------|------------------------------------|
| 1     | -78           | 10                     | 42:1                | 31:1                               |
| 2     | -60           | 20                     | 19:1                | 22:1                               |
| 3     | -40           | 30                     | 2.3:1               | 2.7:1                              |
| 4     | -20           | 40                     | 1:34                | 1:46                               |
| 5     | 0             | 50                     | 1:37                | 1:46                               |
|       |               |                        |                     |                                    |

[a] Time after start of the deprotonation. [b] Values from ref.<sup>[4b]</sup>

#### **Crossover** Experiments

Based on these results, crossover experiments were performed by subjecting a 2:1 mixture of sulfones 2 and  $\alpha$ -D-4 to DoM under the standard conditions (Table 6). Aliquots were taken at defined temperatures and times and quenched with deuterium oxide and water separately at the same time. The ratio of compounds o-D-2,  $\alpha$ -D-2,  $o,\alpha$ -D<sub>2</sub>-4, and  $\alpha$ -D-4 formed on deuteration showed that the initial deprotonation took place at the *ortho*-positions of both 2 and  $\alpha$ -D-4 (entry 1), generating both o-Li-2 and  $\alpha$ -D,o-Li-4 selectively within experimental error based on the formation of o-D-2 and  $o,\alpha$ -D<sub>2</sub>-4 as the strongly dominating

Table 6. Product distribution of the crossover experiment between 2 and  $\alpha$ -D-4.



| Quench by: |                      |      | $D_2O$   | $H_2O$                      |  |
|------------|----------------------|------|--|-----------------------------|--|
| Entry      | t                    | Т    | o-D-2/α-D-2/o,α-D <sub>2</sub> -4/α-D-4 <sup>[b]</sup> | 2/α-D-4/o-D-4 <sup>[b</sup> |  |
|            | [min] <sup>[a]</sup> | [°C] |  |                             |  |
| 1          | 10                   | -78  | >95:<5:>45:<5  | >95:>45:<5                  |  |
| 2          | 20                   | -30  | 50:37:45:5   | >95:>45:<5                  |  |
| 3          | 50                   | -30  | <5:95:32:18  | >95:>45:<5                  |  |

[a] Time refers to the start of the deprotonation. [b] Starting ratio 2/a-D-4, 2:1; compound ratio determined by integration of the <sup>1</sup>H NMR spectra.

products in a 2:1 ratio. The mixture was placed in a bath kept at -30 °C and another aliquot was quenched with D<sub>2</sub>O after 10 min; this experiment revealed that o-Li-2 transmetallated, resulting in the detection of 50% of o-D-2 and 37% of  $\alpha$ -D-2 (entry 2). Moreover 5% of  $\alpha$ -D-4 was detected, whereas the amount of  $o,\alpha$ -D<sub>2</sub>-4 was reduced to 45%. After a further 30 min at -30 °C and deuteration, the amount of o-D-2 became very small, whereas the amount of  $\alpha$ -D-2, with deuterium at the  $\alpha$ -position was almost complete, indicating almost complete *ortho* $\rightarrow \alpha$  transmetalation (entry 3). At the same time, the content of  $\alpha$ -deuterated, but ortho-protonated  $\alpha$ -D-4 increased to 18%, accompanied by a parallel decrease of dideuterated  $o_1\alpha$ -D<sub>2</sub>-4 from 45 to 32%. This result can only be explained by a partial intermolecular proton transfer from the  $\alpha$ -position of *o*-Li-2 to α-D,*o*-Li-4.

The product distribution of  $2/\alpha$ -D-4/o-D-4 on quenching the reaction mixture with water was essentially identical over time, revealing that the deuterium label in  $\alpha$ -D-4 remained in place. This showed that a potential lithium-deuterium transmetalation, which would be manifested by a increase of the proton content in the  $\alpha$ -positions of  $\alpha$ -D-4, did not take place to a significant extent. An experiment using equimolar amounts of 2 and  $\alpha$ -D-4 gave similar results (not shown).

A GC/+CI-MS evaluation of all samples quenched with  $D_2O$  of the crossover experiment revealed the presence of a strongly predominating peak at m/z 270 for o-D- $2/\alpha$ -D-2. The 32:18 ratio of  $o,\alpha$ - $D_2$ - $4/\alpha$ -D-4 was also confirmed by a 2:1 ratio of peaks at m/z 285 and 284 in the GC/+CI-MS spectra. In the mixture quenched with water after 50 min, a peak at m/z 283, indicating the presence of non-deuterated p-tolyl sulfone 4, was detected with only 4% intensity, showing that metalation at the deuterated  $\alpha$ -position of  $\alpha$ -D-4 or transmetalation to the deuterated  $\alpha$ -position of  $\alpha$ -D,o-Li-4 occurred only to a negligible extent.

#### Proton Transfer Equilibria Among ortho- and a-Lithiated Sulfones and the Potential Involvement of Discrete Dilithium Species

The intermolecular proton transfer between *o*-Li-2 and  $\alpha$ -D,*o*-Li-4 observed in the crossover experiment leads to the question: does the process proceed in a concerted manner or stepwise with a discrete *ortho*, $\alpha$ -dilithiosulfone intermediate (cf. Scheme 2). In the latter process the aryllithium *o*-Li-2 acts as the base to abstract the  $\alpha$ -proton of a second molecule of *o*-Li-2, resulting in neutral 2 and dilithium species *o*, $\alpha$ -Li<sub>2</sub>-2 in equilibrium (Scheme 7), which subsequently undergo a thermodynamically favored proton transfer to generate two molecules of  $\alpha$ -Li-2.

To detect the involvement of a potential dilithium intermediate  $o,\alpha$ -Li<sub>2</sub>-2 during the transmetalation process, six of the twelve samples that were quenched by D<sub>2</sub>O during the kinetic run at -50 °C (see above) were investigated by GC/ +CI-MS. If present, a significant concentration of  $o,\alpha$ -D<sub>2</sub>-2 resulting from  $o,\alpha$ -Li<sub>2</sub>-2 should lead to a significant peak enhancement at m/z 271 and at m/z 269 for 2 [M + H]<sup>+</sup>. In



Scheme 7. The potential involvement of dilithiated species  $o_{,\alpha}$ -Li<sub>2</sub>-**2** during transmetalation.

the event, however, the peak at m/z 270, corresponding to the sum of singly deuterated *o*-D-2 and  $\alpha$ -D-2 [M(*o*-D-2/ $\alpha$ -D-2)+H<sup>+</sup>], was strongly predominant in each sample. The intensity of the peak at m/z 271, which should represent the sum of the <sup>13</sup>C isotope peak of *o*-D-2/ $\alpha$ -D-2 and a potential dideuterated compound, showed only the intensity required for the <sup>13</sup>C isotope peak and no further intensity gain, indicating that  $o,\alpha$ -Li<sub>2</sub>-2 was present under the transmetalation conditions only to a very small extent, if at all. The intensity of the peak at m/z 269 was accordingly also very small. Similarly, no evidence for the presence of a dideuterated compound  $o,\alpha$ -D<sub>2</sub>-2 was found on analysis of the products obtained in the crossover experiment (see above).

Because 1.05–1.15 equiv. *n*BuLi was used for the deprotonation of sulfones to assure that the deprotonation proceeded to the highest possible extent, it may be assumed that a quantity of up to  $10\% o, \alpha$ -Li<sub>2</sub>-2 will be cogenerated during deprotonation, which can, in principle, act as a catalyst for the transmetalation (Scheme 8). More reactive  $o, \alpha$ -



Scheme 8. Potential action of  $o,\alpha$ -Li<sub>2</sub>-2 as a catalyst during transmetalation.

Table 7. Transmetalation of o-Li-4 to a-Li-4 in the presence of dilithium intermediate o,a-Li<sub>2</sub>-2.



[a] Separate deprotonation of **2** with 2 equiv. *n*BuLi. [b] Separate deprotonation of **4** with 1 equiv. *n*BuLi. [c] Time 0 refers to mixing of  $o,\alpha$ -Li<sub>2</sub>-**2** with o-Li-**4** at -78 °C. [d] The  $\alpha$ -H signals of o-D-**4** and  $o,\alpha$ -D<sub>2</sub>-**2** are not distinguishable by <sup>1</sup>H NMR spectroscopy. It is assumed that the residual H-content of  $o,\alpha$ -D<sub>2</sub>-**2** is negligible and the decrease of the proton content is due to the transmetalation.

Li<sub>2</sub>-2 may promote proton transfer from the  $\alpha$ -position of o-Li-2, thus regenerating the catalyst  $o,\alpha$ -Li<sub>2</sub>-2 and releasing unreactive  $\alpha$ -Li-2. This cycle would operate until all o-Li-2 is transformed.

To obtain information about the feasibility of this mechanism, the dilithium species  $o_1\alpha$ -Li<sub>2</sub>-2 was individually generated (Table 7, entry 1) and subsequently added to a threefold excess of o-Li-4 generated from tolylsulfone 4 (entry 2). The mixture of  $o,\alpha$ -Li<sub>2</sub>-2 and o-Li-4 remained stable at -78 °C for 10 min, as determined by quenching aliquots by  $D_2O$  and isolation of *o*-D-4 and *o*, $\alpha$ -D<sub>2</sub>-2, resulting from deuteration of o-Li-4 and  $o,\alpha$ -Li<sub>2</sub>-2, respectively (entry 3). The mixture was subsequently warmed in the same time and temperature regime as the individual transmetalation of o-Li-4 to  $\alpha$ -Li-4 (entries 4–7, cf. Table 4). The rearrangement was not accelerated by added  $o,\alpha$ -Li<sub>2</sub>-2, even though it was present in a comparably very high concentration (cf. Table 4). The dianion  $o,\alpha$ -Li<sub>2</sub>-2 remained apparently unchanged during the whole transmetalation, since the D-content of  $o_1\alpha$ -D<sub>2</sub>-2 only decreased to a small extent over time. The reverse experiment, in which the dianion from 4 was added to a solution of o-Li-2 generated from 2, gave similar results (not shown). Thus, the small excess of *n*BuLi with respect to the sulfone can be considered as insignificant for the course of the transmetalation.

A final experiment, which addresses the facility of the subsequent intermolecular proton transfer between dilithiated species  $o,\alpha$ -Li<sub>2</sub>-2 and neutral sulfones 2 was performed (Table 8). Neutral sulfone 4 was added to a solution of  $o,\alpha$ -Li<sub>2</sub>-2, generated by dilithiation at  $-78 \,^{\circ}\text{C},^{[5,7]}$  and the reaction was monitored by <sup>1</sup>H NMR analysis after quenching

with D<sub>2</sub>O. Dilithium intermediate  $o,\alpha$ -Li<sub>2</sub>-2 was stable up to -60 °C, no proton transfer with 4 was observed and  $o,\alpha$ -D<sub>2</sub>-2 was the sole observed product (entries 1–3). On further warming,  $o,\alpha$ -Li<sub>2</sub>-2 deprotonated 4 in the  $\alpha$ -position giving  $\alpha$ -D-2 and  $\alpha$ -D-4 via  $\alpha$ -Li-2 and  $\alpha$ -Li-4, respectively. The *ortho*-position of 4 was not deprotonated during the process. The results show that the rate of proton transfer from 4 to the dilithium intermediate  $o,\alpha$ -Li<sub>2</sub>-2 was, in fact, somewhat slower than the transmetalation of o-Li-4 to  $\alpha$ -Li-4 at a similar concentration (cf. Table 4).

#### Discussion

The mechanism of the previously discovered reversal in the lithiation selectivity of  $\alpha$ , $\gamma$ -branched sufones was investigated in the current study. Several points deserve comment.

Both the *ortho*- and the  $\alpha$ -deprotonation of sufones **2–4** and their deuterated analogues as well as the transmetalation of the resulting *ortho*-sulfonylphenyllithium intermediates display large kinetic isotope effects (Scheme 5, Tables 1, 2, and 3). The intramolecular KIE of monodeuterated sulfone was determined to be 41, which is in the typical range for such processes. For all other metalation processes, an exact determination was not possible because the large rate difference of *ortho*-deprotonation and dedeuteration leads to competitive  $\alpha$ -deprotonation. This is reflected by the fact that *ortho*,*ortho'*-dideuterated sulfone *o*,*o*-D<sub>2</sub>-**2** undergoes *ortho*-dedeuteration and  $\alpha$ -deprotonation competitively (Table 2). The reverse case, in which DoM competes to a significant extent with  $\alpha$ -dedeuteration, was found for Table 8. Transmetalation reaction of the dilithium intermediate derived from 2 with neutral 4.



[a] Separate deprotonation of sulfone 2 with 2 equiv. nBuLi. [b] Time 0 refers to mixing of  $o,\alpha$ -Li<sub>2</sub>-2 with 4 at -78 °C. [c] The  $\alpha$ resonances of  $o.\alpha$ -D<sub>2</sub>-2,  $\alpha$ -D-2 and  $\alpha$ -D-4 cannot be distinguished. Because the  $\alpha$ -D content of  $\alpha$ -D-2 and  $o_1\alpha$ -D<sub>2</sub>-2 does not change, the decrease of the  $\alpha$ -H integral corresponds to the increase of the α-D content of α-D-4.

 $\alpha$ -D-3, although the rate difference was not large enough to induce high metalation selectivity. However the resulting ortho-lithiated species remained stable at low temperature (Table 3). The ortho  $\rightarrow \alpha$  transmetalation proceeds with or*tho,ortho'*, $\alpha$ -trideuterated substrate  $o, o, \alpha$ -D<sub>3</sub>-2, but much slower and at considerably higher temperature than that of sulfone 2 (Table 1).

Free sulfones show a diverse behavior toward metalated sulfones and in transmetalation processes. Sterically relatively unhindered sulfones, such as 3, or its deuterated derivative  $\alpha$ -D-3 protonate or deuterate *o*-Li-2 fast and without a significant energy barrier at -78 °C (Tables S1-S2). This reflects the thermodynamic acidity difference. In contrast, once deprotonated, o-Li-2 displays a significant barrier to proton transfer from sterically hindered y-branched sulfones at low temperature, and it remains stable up to -40 °C even in the presence of large amounts of 2 (Table 5). These results show that the sulfone structure has an important influence on their application as substrates for proton transfers.



The rates of the *ortho* $\rightarrow \alpha$  transmetalation reaction are best described by first-order kinetics, but show a clear concentration dependence. These results suggest that the transmetalation does not proceed through an intramolecular proton transfer as shown in VI, but that a bimolecular course via aggregates VII or alternatively by two-step mechanism via VIII and IV should be followed (cf. Scheme 2). Unfortunately, nothing is known about the aggregation behavior of ortho-lithiated aryl sulfones,<sup>[6]</sup> however  $\alpha$ -sulfonyl carbanions form equilibria of monomers and dimers of varying composition both in the solid state and in solution.[1g,7e,11]

With the crossover experiment using **2** and  $\alpha$ -D-4, it was clearly demonstrated that the ortho $\rightarrow \alpha$  transmetalation takes place at least partly as an intermolecular process (Table 6). The lithiated species o-Li-2 and  $\alpha$ -D,o-Li-4 are stable at -78 °C, but undergo the transmetalation with different rates because of their differing kinetic isotope effects at -30 °C (ref.<sup>[4b]</sup> vs. Scheme 6). An intermolecular proton transfer from the a-position of o-Li-2 to a-D,o-Li-4 was clearly established by the formation of significant amounts of  $\alpha$ -D-4 (Table 6). This result further decreases the likelihood of an intramolecular transmetalation process via VI (cf. Scheme 2).

At this stage, two pathways for the intermolecular proton transfer process from o-Li-2 to  $\alpha$ -Li-2 remain (cf. Scheme 2). It may occur by concerted proton transfer of two monomeric aryllithium units via a transition state similar to VII. Alternatively, a dimeric aggregate may also account for the process. Both pathways display concentration dependence, but involve only the concentration of one species.

However, an alternative stepwise mechanism may, in principle, also account for product formation, in which lithiated sulfone o-Li-2 deprotonates a second o-Li-2 intermediate, resulting in free 2 and *ortho*, $\alpha$ -sulforyl dilithium intermediate  $o,\alpha$ -Li<sub>2</sub>-2 (Scheme 7). Several results exclude the dilithium intermediate from the mechanistic options. First, the transmetalation proceeds in the presence of a large excess of free sulfone 2, which prevents the formation of  $o,\alpha$ -Li<sub>2</sub>-2, with the same rate (Table 5).

Second, if  $o,\alpha$ -Li<sub>2</sub>-2 was present in significant concentrations it should be detectable by mass spectrometry. However, dideuterated compounds were not detected by GC/ +CI-MS monitoring of the D<sub>2</sub>O quenched product mixtures of several transmetalation reactions. These results do not support the double proton transfer pathway via  $o_{,\alpha}$ -Li<sub>2</sub>-2, however, it also does not exclude it conclusively.

Third, the potential action of  $o_{,\alpha}$ -Li<sub>2</sub>-2 as a catalyst is not supported by the results, because the transmetalation process is not influenced with respect to its time and temperature profile, even in the presence of large amounts of dilithiated species (Scheme 8, Table 7). Thus,  $o,\alpha$ -Li<sub>2</sub>-2 is not competent to accelerate the *ortho* $\rightarrow \alpha$  transmetalation; it would be at maximum an innocent bystander in case it is generated. It was also shown that the subsequently mandatory proton transfer from  $o,\alpha$ -Li<sub>2</sub>-2 to 4 is even somewhat slower than the transmetalation of 2 or 4 (see Table 8 vs.

1

2

3

Tables 4 and 5). Based on these results, the involvement of dilithium intermediates in the transmetalation process can be considered unlikely.

Thus, based on the experimental evidence, it is most likely that the *ortho* $\rightarrow \alpha$  transmetalation of  $\alpha, \gamma$ -branched sulfones, such as **2** or **4**, proceeds through an intermolecular concerted process either via transition state **5** or from a similar dimeric aggregate (Scheme 9).



Scheme 9. Mechanistic proposal for the *ortho* $\rightarrow \alpha$ -transmetalation of lithiated **2**.

#### Conclusions

The previously described surprising reversal of the deprotonation selectivity of  $\alpha,\gamma$ -branched alkyl phenyl sulfones bearing a-hydrogen atoms toward DoM is based on the limited steric accessibility of the  $\alpha$ -hydrogen atoms by organolithium bases and the parallel operation of the complex-induced proximity effect. Here, the mechanism of the transmetalation of the resulting ortho-sulfonylphenyllithium to the thermodynamic  $\alpha$ -sulfonyl carbanions was studied in detail. Significant kinetic isotope effects were observed for both the initial deprotonation and the ortho $\rightarrow \alpha$  transmetalation. Although not studied in detail here, deuterated precursors may be used to steer the metalation selectivity. The kinetics of the transmetalation were determined. A better fit to first-order kinetics was found, but a contrasting concentration dependence of the rate was observed. The study of proton transfer equilibria between the different ortho-sulfonylaryllithium intermediates showed that the transmetalation is fast with unhindered free sulfones, but does not proceed with more hindered  $\alpha, \gamma$ -branched sulfones such as 2 or 4 at low temperature. Crossover experiments provided conclusive evidence that the transmetalation takes an intermolecular course. Two possibilities of such an intermolecular process were investigated. A stepwise procedure via dilithiated intermediates was discarded because the individually generated dilithium species did not influence the course of the transmetalation reactions. Thus, it is most likely that the transmetalation proceeds by an intermolecular concerted or aggregate-based process, which has a high enough activation barrier that both the ortho-sulfonylaryllithium as well as the  $\alpha$ -sulfonylalkyllithium intermediates can be reliably applied as synthetic intermediates. The processes described here may also be observed in other compound classes such as phosphine oxides, sulfides, or sulfoxides. Such processes are being investigated in these laboratories and results will be reported in due course.

#### **Experimental Section**

For general information see the Supporting Information. Compounds **2–4** are known compounds that have been characterized previously.<sup>[13]</sup> Dialkylated sulfones **2** and **3** were prepared according to a reported procedure.<sup>[4b]</sup>

2,6-Dimethylhept-4-yl 4-Methylphenyl Sulfone (4):<sup>[13]</sup> nBuLi (1.6 M in hexane, 6.56 mL, 10.5 mmol) was added dropwise to a stirred solution of 4-(methylsulfonyl)toluene (1.7 g, 10 mmol) and TMEDA (3 mL, 19.5 mmol) in anhydrous THF (50 mL) at -78 °C under a nitrogen atmosphere. After stirring for 10 min, isobutyl iodide (1.03 mL, 10.5 mmol) was added dropwise at -78 °C. After stirring for 10 min, the reaction mixture was warmed to 0 °C during 1 h. The reaction mixture was cooled to -78 °C and TMEDA (3 mL, 19.5 mmol) and *n*BuLi (1.6 M in hexane, 6.56 mL, 10.5 mmol) were added dropwise. After 5 min, isobutyl iodide (1.03 mL, 10.5 mmol) was added, the solution was stirred at -78 °C for 30 min, warmed to 0 °C during 1 h and stirred until the reaction was complete, as indicated by TLC. The reaction mixture was quenched with a saturated NH<sub>4</sub>Cl solution, the layers were separated and the aqueous layer was extracted with diethyl ether (3  $\times$ 50 mL). The combined organic extracts were washed with brine, dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. Purification by column chromatography (EtOAc/hexane, 1:40 to 1:10) gave 4 (2.23 g, 79%) as a colorless solid. The analytical data were consistent with reported data.<sup>[13]</sup>

ortho-Deuteration of Sulfones 2, o-D-2 and  $\alpha$ -Deuteration of 3. General Procedure: *n*BuLi (1.6 M in hexane, 0.75 mL, 1.15 mmol, or 0.82 mL, 1.3 mmol) was added dropwise to a stirred solution of sulfone 2, o-D-2, or 3 (1 mmol) and TMEDA (0.3 mL, 1.95 mmol) in anhydrous THF (5 mL) at -78 °C under a nitrogen atmosphere. After stirring for 10 min, D<sub>2</sub>O (0.5 mL) was added. The reaction mixture was warmed to room temperature and diluted with water (2 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. Purification by column chromatography (EtOAc/hexane, 1:20) gave deuterated sulfones *o*-D-2, *o*,*o*-D<sub>2</sub>-2, or  $\alpha$ -D-3.

**2,6-Dimethylhept-4-yl 2-Deuteriophenyl Sulfone** (*o*-**D**-**2**): Yield 266 mg (98%); 96% *ortho*-**D**; colorless crystals; m.p. 48–49 °C;  $R_{\rm f}$  = 0.47 (EtOAc/hexane, 1:5). IR:  $\tilde{v}$  = 2968, 2933, 2879, 1472, 1444, 1439, 1374, 1316, 1300, 1154, 1128, 1085, 914, 784, 760, 733 cm<sup>-1</sup>. MS (ESI<sup>+</sup>): *m/z* (%) = 270 (100) [M + H<sup>+</sup>], 144 [ArSO<sub>2</sub>H + H<sup>+</sup>]. HRMS (CI<sup>+</sup>): *m/z* calcd. for C<sub>15</sub>H<sub>24</sub>D<sub>2</sub>O<sub>2</sub>S<sup>+</sup> [M + H<sup>+</sup>] 270.1638; found 270.1632. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.73 (d, *J* = 6.2 Hz, 6 H), 0.82 (d, *J* = 6.2 Hz, 6 H), 1.24 (m, 2 H), 1.64 (m, 4 H), 2.96 (m, 1 H), 7.50 (m, 2 H), 7.58 (m, 1 H), 7.81 (m, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.0 (q), 23.0 (q), 25.7 (d), 38.7 (t), 61.1 (d), 129.0 (d), 129.1 (d), 133.6 (d), 138.0 (s) ppm.

**2,6-Dimethylhept-4-yl 2,6-Dideuteriophenyl Sulfone** (*a,o*-**D**<sub>2</sub>-2): Yield 265 mg (98%); 92% *ortho*-D; colorless crystals; m.p. 48– 49 °C.  $R_{\rm f}$  = 0.46 (EtOAc/hexane, 1:5). IR:  $\tilde{v}$  = 3063, 2958, 2935, 1573, 1432, 1387, 1369, 1314, 1296, 1213, 1152, 771 cm<sup>-1</sup>. MS (ESI<sup>+</sup>): *m/z* (%) = 563 (20) [2M + Na<sup>+</sup>], 293 (100) [M + Na<sup>+</sup>]. HRMS (ESI<sup>+</sup>): *m/z* calcd. for C<sub>15</sub>H<sub>23</sub>D<sub>2</sub>O<sub>2</sub>S<sup>+</sup> [M + H<sup>+</sup>] 271.1695; found 271.1697. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.72 (d, *J* = 6.1 Hz, 6 H), 0.81 (d, *J* = 6.2 Hz, 6 H), 1.21 (m, 2 H), 1.60 (m, 4 H), 2.93 (m, 1 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 7.80 (m, 8% H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.9 (q), 22.9 (q), 25.6 (d), 38.6 (t), 61.0 (d), 128.9 (d), 133.5 (d), 137.9 (s) ppm.

(4-Deuterio-2,6-dimethylhept-4-yl) 2,6-Dideuteriophenyl Sulfone (0,0,a-D<sub>3</sub>-2): *n*BuLi (1.6 M in hexane, 2.7 mL, 4.3 mmol) was added

dropwise to a stirred solution of sulfone  $o_1o_2-2$  (992 mg, 3.7 mmol) and TMEDA (1 mL, 6.5 mmol) in anhydrous THF (4 mL) at -20 °C under a nitrogen atmosphere. After stirring for 10 min, D<sub>2</sub>O (0.5 mL) was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether ( $3 \times 20$  mL). The combined organic extracts were washed with brine, dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. Purification by short column chromatography (EtOAc/hexane, 1:20) gave o,o,α-D<sub>3</sub>-2 (901 mg, 90%; 96% ortho-D, 100% α-D) as colorless crystals; m.p. 48–49 °C;  $R_{\rm f} = 0.48$  (EtOAc/hexane, 1:5). IR:  $\tilde{v} = 2967, 2941, 2879,$ 1473, 1437, 1312, 1299, 1154, 1114, 838, 760, 724 cm<sup>-1</sup>. MS (ESI<sup>+</sup>): m/z (%) = 565 (20) [2M + Na<sup>+</sup>], 294 (100) [M + Na<sup>+</sup>]. HRMS (ESI<sup>+</sup>): m/z calcd. for C<sub>15</sub>H<sub>21</sub>D<sub>3</sub>O<sub>2</sub>SNa<sup>+</sup> [M + Na<sup>+</sup>] 294.1578; found 294.1579. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 0.76$  (d, J =6.1 Hz, 6 H), 0.85 (d, J = 6.3 Hz, 6 H), 1.26 (m, 2 H), 1.66 (m, 4 H), 7.53 (m, 2 H), 7.61 (m, 1 H), 7.85 (m, 4% H) ppm. <sup>13</sup>C NMR  $(100 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 22.1 \text{ (q)}, 23.0 \text{ (q)}, 25.7 \text{ (d)}, 38.7 \text{ (t)}, 129.0 \text{ (q)}$ (d), 133.6 (d), 138.1 (s) ppm.

**3-Deuteriopent-3-yl Phenyl Sulfone** (*a*-**D**-3): Yield 210 mg (99%); 100% D; colorless crystals; m.p. 47–48 °C;  $R_{\rm f}$  = 0.57 (EtOAc/hexane, 1:5). IR:  $\tilde{v}$  = 2980, 2949, 2890, 1467, 1451, 1305, 1158, 1140, 1084, 736, 726, 694, 612 cm<sup>-1</sup>. MS (ESI<sup>+</sup>): *m/z* (%) = 236 (100) [M + Na<sup>+</sup>]. HRMS (ESI<sup>+</sup>): *m/z* calcd. for C<sub>11</sub>H<sub>15</sub>DO<sub>2</sub>SNa<sup>+</sup> [M + Na<sup>+</sup>] 236.0826; found 236.0825. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.00 (t, *J* = 7.5 Hz, 6 H), 1.69 (dq, *J* = 7.5, 15.1 Hz, 2 H), 1.87 (dq, *J* = 7.5, 15.1 Hz, 2 H), 7.26 (m, 2 H), 7.62 (m, 1 H), 7.89 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.3 (q), 20.4 (t), 66.8 [s (d, *J* = 20.7 Hz)], 128.9 (d), 129.3 (d), 133.6 (d), 138.6 (s) ppm.

4-Deuterio-2,6-dimethylhept-4-yl 4-Methylphenyl Sulfone (α-D-4): nBuLi (1.6 м in hexane, 2.7 mL, 4.3 mmol) was added dropwise to a stirred solution of sulfone 4 (1.04 g, 3.7 mmol) and TMEDA (1 mL, 6.5 mmol) in anhydrous THF (4 mL) at -20 °C under a nitrogen atmosphere. After stirring for 10 min, D<sub>2</sub>O (0.5 mL) was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3  $\times$  20 mL). The combined organic extracts were washed with brine, dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. Purification by short column chromatography (EtOAc/ hexane, 1:20) gave α-D-4 (1.04 g, 99%; 100% D) as colorless crystals; m.p. 77–78 °C;  $R_{\rm f} = 0.76$  (EtOAc/hexane, 1:5). IR:  $\tilde{v} = 2967$ , 2939, 2878, 1600, 1472, 1391, 1374, 1315, 1303, 1291, 1144, 1135, 1089, 822, 731, 722, 696 cm<sup>-1</sup>. MS (CI<sup>+</sup>): m/z (%) = 284 (80) [M +  $H^+$ ], 185 (40) [M - H<sub>2</sub>C=C(CH<sub>3</sub>)<sub>2</sub> - *i*Pr + H<sup>+</sup>], 157 (100)  $[CH_3C_5H_4SO_2H_2^+]$ . HRMS (EI): *m*/*z* calcd. for  $C_{16}H_{25}DO_2S^+$  [M<sup>+</sup>] 283.1716; found 283.1715. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 0.74$ (d, J = 6.2 Hz, 6 H), 0.82 (d, J = 6.3 Hz, 6 H), 1.22 (m, 2 H), 1.64 (m, 4 H), 2.39 (s, 3 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.68 (d, J =8.0 Hz, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.6 (q), 22.0 (q), 22.9 (q), 25.6 (d), 38.6 (t), 129.0 (d), 129.6 (d), 135.0 (s), 144.3 (s) ppm.

Kinetic Study of the Transmetalation of 2: TMEDA (0.3 mL, 2 mmol) and *n*BuLi (1.6 M in hexane, 0.72 mL, 1.15 mmol) were added to a stirred solution of sulfone 2 (268 mg, 1 mmol) in anhydrous THF (12 mL) at the given temperature. After the given time (Supporting Information, Tables S3–7), an aliquot of the solution was removed by using a syringe and added to a capped dry vial containing a few drops of  $D_2O$ . The volume of the sample corresponded to the total volume divided by the number of taken samples. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO<sub>4</sub>, filtered, evaporated, and the residue was analyzed by <sup>1</sup>H NMR spectroscopy. The procedure

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was repeated. The raw data are listed in Tables S3–7. For generation of Figure 1, the individual data points were transformed from real percentage of deuterated *o*-D-2/ $\alpha$ -D-2 to ideal 100% deuteration degree; e.g., isolated *o*-D-2/ $\alpha$ -D-2 with a 95% deuteration degree, ratio 9.6:1, which corresponds to 86% *o*-D-2 and 9%  $\alpha$ -D-2 was transformed to 100% D content at a 9.6:1 ratio = 90.5% *o*-D-2 and 9.5%  $\alpha$ -D-2. The values in the tables are the average values calculated from at least three kinetic measurements at every temperature.

Determination of the Intramolecular Kinetic Isotope Effect at *o*-D-2: See Scheme 5. *n*BuLi (1.6 M in hexane, 62  $\mu$ L, 0.1 mmol) was added dropwise to a stirred solution of sulfone *o*-D-2 (30 mg, 0.11 mmol) and TMEDA (0.03 mL, 0.2 mmol) in anhydrous THF (1 mL) at -78 °C under a nitrogen atmosphere. After stirring for 5 min, a sample was removed by using a syringe and quenched with H<sub>2</sub>O, and a second sample with D<sub>2</sub>O (0.5 mL). The products were extracted with diethyl ether (2 mL) and the organic extracts were dried with MgSO<sub>4</sub>, filtered, evaporated, and the residue was analyzed by <sup>1</sup>H NMR spectroscopy.

Transmetalation of 4 and Deuterated Compounds o,o-D<sub>2</sub>-2, o,o,a-D<sub>3</sub>-2, a-D-3 and a-D-4. General Procedure: See Tables 1, 2, 3, and 4, Scheme 6. TMEDA (0.15 mL, 1 mmol) and *n*BuLi (1.6 M in hexane, 0.344 mL, 0.55 mmol) were added to a stirred solution of sulfone 4 or o,o-D<sub>2</sub>-2,  $o,o,\alpha$ -D<sub>3</sub>-2,  $\alpha$ -D-3, or  $\alpha$ -D-4 (0.5 mmol) in anhydrous THF (3–5 mL) at –78 °C. After the given time (Tables 1, 2, 3, and 4) an aliquot of the solution was removed by using a syringe and added to a capped vial containing a few drops of D<sub>2</sub>O or H<sub>2</sub>O. The volume of the sample corresponded to the total volume divided by the number of samples taken. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO<sub>4</sub>, filtered, evaporated, and the residue was analyzed by <sup>1</sup>H NMR spectroscopy. The procedure was repeated as described in the tables.

ortho- to  $\alpha$ -Transmetalation of 2 Using 0.5 equiv. of Base and Deuteration: See Table 5. TMEDA (0.07 mL, 0.5 mmol) and *n*BuLi (1.6 M in hexane, 156 µL, 0.25 mmol) were added to a stirred solution of sulfone 2 (134 mg, 0.5 mmol) in THF (5 mL) at -78 °C. The further procedure was identical to the general procedure for the transmetalation of deuterated compounds.

**Crossover Reaction of 2 and \alpha-D-4:** See Table 6. TMEDA (0.15 mL, 1 mmol) and *n*BuLi (1.6 M in hexane, 0.363 mL, 0.58 mmol) were added to a stirred solution of sulfone **2** (86 mg, 0.33 mmol) and  $\alpha$ -D-4 (45 mg, 0.165 mmol) in anhydrous THF (3 mL) at -78 °C. After 10 min, an aliquot of the solution was removed by using a syringe and added to a capped vial containing a few drops of D<sub>2</sub>O or H<sub>2</sub>O. The sample volume corresponded to the total volume divided by the number of samples taken. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO<sub>4</sub>, filtered, evaporated, and the residue was analyzed by <sup>1</sup>H NMR spectroscopy.

ortho- to  $\alpha$ -Transmetalation of *o*-Li-4 in the Presence of  $o,\alpha$ -Li<sub>2</sub>-2: See Table 7. The two deprotonations were performed in separate flasks. *n*BuLi (1.6 M in hexane, 0.164 mL, 0.26 mmol) was added dropwise to a stirred solution of sulfone 2 (34 mg, 0.13 mmol) and TMEDA (0.1 mL, 0.65 mmol) in anhydrous THF (1 mL) at -40 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 30 min and cooled to -78 °C. In the meantime, *n*BuLi (1.6 M in hexane, 0.247 mL, 0.39 mmol) was added dropwise to a stirred solution of sulfone 4 (106 mg, 0.38 mmol) and TMEDA (0.1 mL, 0.65 mmol) in anhydrous THF (3 mL) at -78 °C under a nitrogen atmosphere in another flask. The reaction mixture containing  $o,\alpha$ -Li<sub>2</sub>-2 was added by cannula to the flask containing *or*-

*tho*-deprotonated sulfone 4 at -78 °C. After 10 min at this temperature, a sample (1 mL) was taken by using a syringe and added to a dry capped vial containing a few drops of D<sub>2</sub>O. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. The remaining reaction mixture was placed in a bath at -60 °C and kept for 10 min. Another sample (1 mL) was removed and deuterated as described above. The procedure was repeated at -40, -20, and 0 °C. The mass balance was determined to be quantitative for each mixture and the products were analyzed by <sup>1</sup>H NMR spectroscopy.

Proton Transfer from 4 to *o*,α-Li<sub>2</sub>-2: See Table 8. TMEDA (0.15 mL, 1 mmol) and *n*BuLi (1.6 м in hexane, 275 µL, 0.44 mmol) were added to a stirred solution of sulfone 2 (54 mg, 0.2 mmol) in THF (3 mL) at -40 °C. After 30 min, 0.5 mL of the solution was taken by using a syringe and added to a dry capped vial containing a few drops of D<sub>2</sub>O. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO<sub>4</sub>, filtered, and the solvents evaporated. The reaction mixture was cooled to -78 °C and sulfone 4 (47 mg, 0.17 mmol) was added. After stirring for 10 min, 0.5 mL of the solution was removed by using a syringe and added to a dry capped vial containing a few drops of D<sub>2</sub>O. The product was extracted with diethyl ether (2 mL) and the organic extract was dried with MgSO4, filtered, and the solvents evaporated. The remaining reaction mixture was placed in a bath at -60 °C and kept for 10 min. Another sample (0.5 mL) was removed and deuterated as described above. The procedure was repeated at -40, -20, and 0 °C. The mass balance was determined to be quantitative for each mixture and the product mixtures were analyzed by <sup>1</sup>H NMR spectroscopy.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, analytical data for all compounds, raw data of kinetic and crossover measurements, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds.

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