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Synthetic Methods

Solvent Choice and Kinetic Isotope Effects (KIEs) Dramatically Alter Regioselectivity in the Directed *ortho* Metalation (DoM) of 1,5-Dichloro-2,4-dimethoxybenzene

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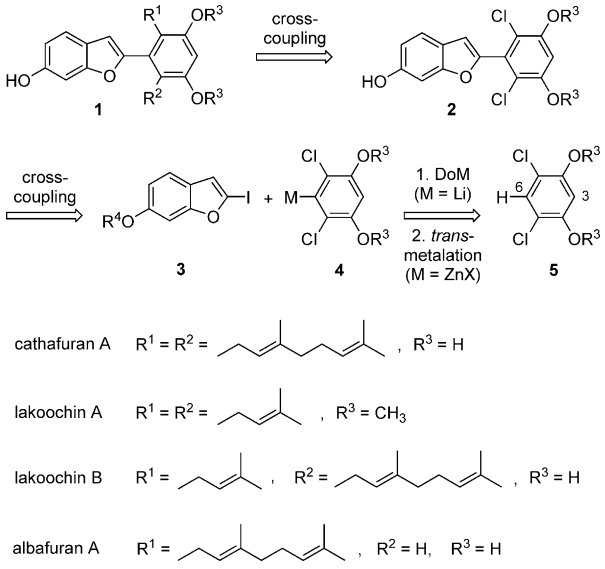
Abstract: The regioselective formation of the 6-lithio derivative of 1,5-dichloro-2,4-dimethoxybenzene (i.e., **12**) by directed *ortho* metalation (DoM) with *n*BuLi in THF is described. Although literature reports suggest direct deprotonation at C6, a series of time-course and labelling studies has revealed that deprotonation rather occurs exclusively at C3 followed by isomerization of the anion to C6. By contrast, when DoM was performed in Et_2O, deprotonation again occurred selectively at C3, but now no isomerization occurs, and electrophilic capture produces the regioisomer of that produced in THF. In these labeling studies, it has been found that deuterium has an enormous kinetic isotope effect (KIE) that suppresses not only the original DoM reaction at C3 when deuterium is present there, but also suppresses isomerization to C6 when the label is at that site. Remarkably, this "protecting-group" role of the deuterium is unique to THF; in ether, full deprotonation of the deuterium at C3 was observed.



Scheme 1. Natural products obtainable from a central DoM reaction of 1,5-dichloro-2,4-resorcinol derivatives (**5**).

Directed *ortho* metalation (DoM)[1,2] is a powerful tool to prepare aryl products of considerable complexity in an efficient manner by eliminating the need for a highly functionalized precursor, such as the corresponding halide, thus, reducing step count and minimizing waste.[3] Although the primary use of DoM has been to trap the aryllithium directly with electrophiles by nucleophilic substitution, transmetalation has also been shown as an effective pathway into cross-coupling chemistry.[4] This approach appealed to us when we considered a general strategy to prepare members of the benzofuran catechol-based family of natural products shown in Scheme 1. Based on a report by Kraus and Zeng,[5] we felt that **5** could be deprotonated at C6 to provide the lithium salt **4** selectively that following transmetalation to the corresponding zinc derivative would be amenable for selective cross-coupling with the iodide center in **3**. Subsequent stereo- and regioselective cross-coupling with the requisite terprenylborate would give the desired final targets using methodology worked out in our laboratories by using our Pd-PEPPSI (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation) precatalysts.[6] In the course of these studies, we have uncovered a dramatic solvent effect on the selectivity of the DoM process, which in turn has revealed some interesting insights into the creation of kinetic and thermodynamic aryl anions.

We began our DoM study by lithiating **6** with *n*BuLi in THF at $-78\,^{\circ}C$ for 30 minutes and quenching with I_2 or CD_3OD (Table 1, entries 1 and 5, respectively). As was observed by Kraus and Zeng,[5] the only products isolated were those resulting from substitution at C6 between the two chlorides (e.g., **7**), which had led them to conclude that this was also the site of deprotonation. Although *ortho* lithiation between two chlorides is with precedent,[7] we wondered if it was not more likely that deprotonation was occurring at C3 between the methoxy groups kinetically and then the resultant anion (i.e., **11**, Scheme 2) was actually isomerizing to the other site (i.e., **12**). There are two competing effects operating herein. The methoxy groups are better templaters[3] that would direct lithiation between them, but the site between the two chlorides is more acidic.

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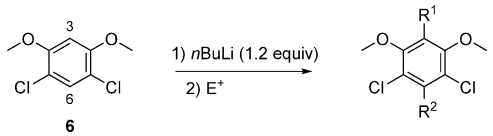
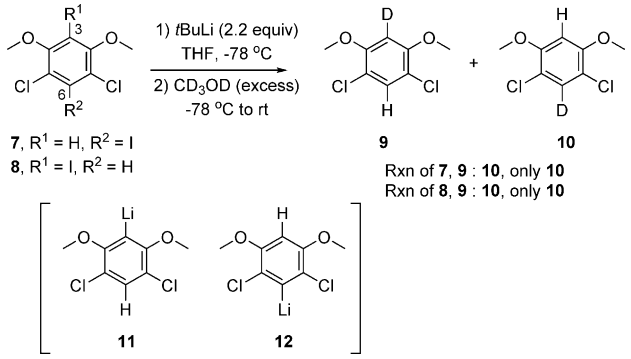
Table 1. DoM of **6** and electrophilic capture in THF and Et_2O.



6

Entry	Solvent	T [°C]	E	R^1	R^2	Product yield [%][a]
1	THF	−78	I_2	H	I	**7** (90)
2	Et_2O	−78	I_2	H	H	**6** (88)[b]
3	Et_2O	25	I_2	I	H	**8** (66)
4	Et_2O	25	CD_3OD	D	H	**9** (75)
5	THF	−78	CD_3OD	H	D	**10** (80)

[a] Yields are reported for isolated products following silica-gel chromatography. [b] Represents recovered starting material (**6**).

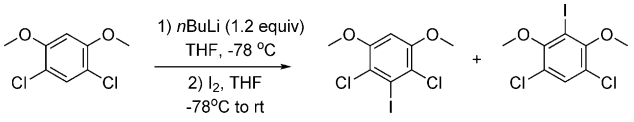


Scheme 2. Determination of the thermodynamically more stable anion of **6** through isomerization studies in THF by Li/I exchange at C6 (**7**) and C3 (**8**).

To address this, we prepared compounds **7** and **8** (Scheme 2) and reacted them under metal/halogen exchange conditions with *t*BuLi, which is necessary to avoid quenching/alkylation problems associated with the *n*BuI by-product of the exchange with *n*BuLi. Lithiation of **8**, after quenching, revealed that under nearly identical reaction conditions that the DoM reactions were carried out, isomerization of **11** to anion isomer **12** was complete. This is consistent with the possibility that in THF **12** is the thermodynamically more stable anion and deprotonation between the methoxy groups occurs first. In support of this, lithiation of **7** resulted solely in electrophilic capture at the site between the chlorides (i.e., **10**). Thus, one can say that the more stable anion resides at C6 and this is also supported by computation (vide infra).

To get a feel for the rates involved in the various processes described above, time-course studies were conducted. Deprotonation was followed with **6** (Table 2) and was found to be not fast at −78 °C, because roughly 20% of **6** remained after one minute (entry 4). However, this study did reveal that deprotonation does indeed occur between the methoxy groups (C3), at least to some extent, and that isomerization does in fact occur and that it is very fast. In entry 1, the quench with I_2 was done immediately following the last drop of *n*BuLi. Assuming for now that deprotonation only occurs at C3, isomerization of **11** to **12** is clearly very rapid.

Table 2. Regioselective lithiation of 1,5-dichloro-2,4-dimethoxybenzene (**6**) with *n*BuLi: a kinetic study.



6 **7** **8**

Entry	t [s][a]	Product Distribution[b] **7**	**8**	**6**	**7/8**
1	0.5	31	5	64	6.2:1
2[c]	0.5	31	6	63	5.2:1
3	30	59	2	39	29.5:1
4	60	79	2	19	39.5:1

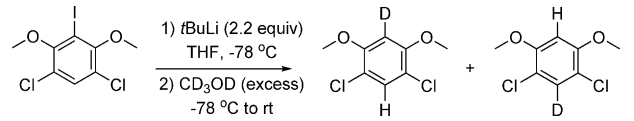
[a] Time that solution was stirred following addition of *n*BuLi and prior to the addition of I_2. [b] Ratios were determined by ^{1}H NMR spectroscopy on crude reaction mixtures. [c] TMEDA (1.2 equiv) was mixed with *n*BuLi and stirred for 5 min prior to being added to solution of **6**.

To examine how fast isomerization truly is, we turned back to the lithium/halogen exchange because it operates at near diffusion-limited rates (Table 3). In this way, **11** could be generated immediately and completely, thus allowing isomerization to be more meaningfully tracked. When the reaction was quenched, just after the last drop of *t*BuLi was added, all of **8** was consumed and isomerization to **12**, which leads to **10**, had proceeded to approximately 70% (entry 1). Isomerization then clearly slows as it takes one full hour to complete conversion to **10** (entries 3, 5, 6), which is suggestive that isomerization occurs by an intermolecular mechanism (vide infra). Temperature is a significant factor, as the same isomerization study at −100 °C, rather than −78 °C, showed far less isomerization at identical time intervals (e.g., see entries 2 vs. 1 and 4 vs. 3).

Solvent effects

Anion stability is greatly influenced by solvent, so we were encouraged to look at the DoM process in a lower dielectric/co-

Table 3. Lithium–halogen exchange of 1,5-dichloro-3-iodo-2,4-dimethoxybenzene (**8**) with *t*BuLi: a kinetic study.



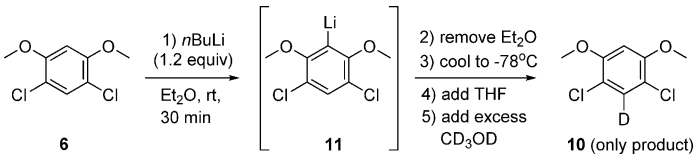
8 **9** **10**

Entry	t[a]	Product distribution[b] **9**	**10**	**8**	**9/10**
1	0.5 s	28	72	0	1:2.6
2	0.5 s[c]	47	53	0	1:1.1
3	30 s	20	78	2	1:3.9
4	30 s[c]	43	57	0	1:1.3
5	30 min	20	80	0	1:4
6	60 min	0	100	0	0:1

[a] Time that solution stirred following addition of *t*BuLi and prior to the addition of CD_3OD. [b] Ratios were determined by ^{1}H NMR spectroscopy on crude reaction mixtures. [c] Reactions were performed at −100 °C.

ordinating solvent. When **6** was lithiated and quenched at −78 °C in Et_2O, no apparent reaction took place (Table 1, entry 2). However, when lithiation was conducted at room temperature, complete consumption of starting materials was observed, but remarkably only the quenched products of anion **11** were observed (entries 3 and 4). This constitutes a complete reversal of regioselectivity compared to when the identical reactions were conducted in THF. Although there are a number of examples in the literature when such an abrupt change in DoM regioselectivity was observed, they involve highly coordinating solvents and additives, such as hexamethylphosphoramide (HMPA) or tetramethylethylenediamin (TMEDA) that significantly alter the organolithiums ability to template to directing groups.[8,9] When TMEDA was added to the DoM reaction of **6** in THF, there was no change in regioselectivity from that observed with THF alone (Table 2, entry 2 vs. 1). Further, we also found that when TMEDA was added to the DoM reaction of **6** in Et_2O, again there was no change in regioselectivity (i.e., the product obtained was from the anion at C3). Thus, the regiochemical change observed in the present study with two similar etheral solvents appears to be without precedent and the DoM selectivity observed is unique when compared with other reports of solvent changes (e.g., TMEDA) in the literature.[8,9]

Although this solvent effect is a very important discovery for synthetic purposes, it also offers an interesting mechanistic puzzle. For example, does the site of deprotonation change in ether, is it a solubility issue when the reaction in Et_2O becomes heterogeneous following deprotonation, or does the thermodynamic anion stability change that dramatically in the two solvents? To address these questions, deprotonation was first conducted at room temperature in Et_2O, which leads exclusively to anion **11** (Scheme 3). Thirty minutes after the addition of



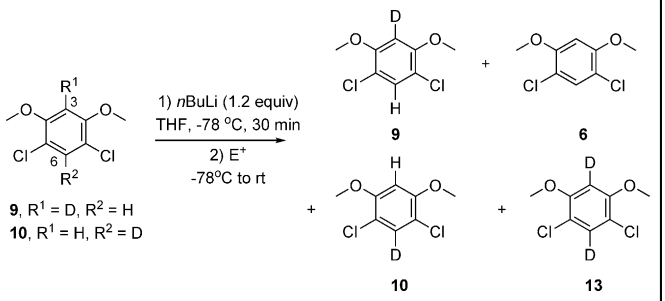
Scheme 3. Exchange of THF for Et_2O following the DoM of **6**.

*n*BuLi, the solvent was carefully removed anaerobically, the flask cooled to −78 °C, and then THF was added. After stirring for an additional 60 minutes, the reaction was quenched with CD_3OD and the only product obtained (i.e., **10**) was derived from the complete isomerization of **11** to **12**. Thus, when **11** was formed completely in Et_2O, there was now no doubt that **6** was not involved in the conversion of **11** to **12** in THF and that THF is unquestionably the trigger for isomerization.

Isotope effects

In an attempt to ascertain details about the mechanism of the deprotonation/isomerization sequence, deuterium-labeled starting materials were prepared and used in the DoM reaction (Table 4). Compound **9** possessing a deuterium between the two methoxy groups was reacted with *n*BuLi in the usual way, and after stirring for 30 minutes was quenched with methanol (entry 1). Evaluation of the reaction mixture revealed that only **9** was present, which on first glance might give the impression that no deprotonation occurred owing to a pronounced kinetic isotope effect (KIE).

Table 4. Effect of deuterium KIE on DoM of compounds **9** and **10**.

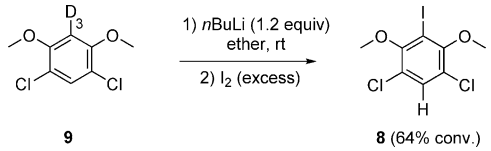


Entry	Starting	E^+	Product distribution[a] 6	9	10	13
1	**9**	CH_3OH	0	100	0	0
2	**10**	CH_3OH	15	0	85	0
3	**9**	CD_3OD	0	0	0	100
4	**10**	CD_3OD	0	0	15	85

[a] Product distributions and ratios were determined by ^1H NMR spectroscopy on the crude reaction mixtures.

When compound **10** was treated under the same reaction conditions, again, mostly the starting material was returned following the methanol quench (entry 2). Although the course of events with **9** was uncertain, there is little reason to suspect that DoM at C3 in **10** had not taken place, but now without the normally spontaneous rearrangement due to another KIE for the deuterium at C6. The significant, reaction-path-altering KIE at C3 supports the possibility that **9** may in fact have been deprotonated, but at C6 and not at C3.[10] To further probe the mechanism, we repeated these two reactions, but now quenched with a deuterium source instead of hydrogen to more effectively track reaction progress. Indeed, when the reaction with **9** was quenched with CD_3OD, full incorporation of a second deuterium occurred, leading to **13** confirming that the deuterium "protected" C3 and DoM did occur now selectively at C6 (entry 3). The complementary experiment was also done on **10** (entry 4), which did confirm, as was expected, that the deuterium at C6 had no effect on normal DoM at C3, and **13** was produced.

In a very surprising result, we found that despite the clearly huge KIE mentioned above (and discussed further below) associated with the deprotonation of the H/D at C3 on **6**/**9**, it is dramatically solvent dependent. Although the deuterium blocked deprotonation of **9** in THF, leading *n*BuLi instead to deprotonate at C6 (Table 4, entries 1 and 3), the same reaction in Et_2O led to exclusive deprotonation of the deuterium (Scheme 4). To the best of our knowledge, there is one exam-



9 **8** (64% conv.)

Scheme 4. Deprotonation of the C3 deuteron in compound **9** by *n*BuLi in ether at RT.

ple in the literature, in which the kinetic DoM site was retained, when the hydrogen was replaced by a deuterium, despite a pronounced KIE.[9] However, in that instance, it was the unique properties of the unusual ethoxyvinyllithium base, relative to conventional alkyllithiums that was attributed to that unanticipated outcome. In the current example, it is almost inconceivable that two solvents of such similar structure and dielectric (ε values for THF and Et_2O are 7.6 and 4.3, respectively) could have such a profound effect to overcome the large KIE at C3 on **9**.[11]

Computational studies

M062X and G3MP2B3 calculations were carried out on the deprotonation of **6** by LiMe as a model for DoM to reduce computational time required to deal with the conformers of *n*BuLi.[12] The data presented in Table 5 for deprotonation were

Table 5. Thermodynamic parameters for important structures for the lithiation reaction of **6** at C6 to form **12** and C3 to form **11**.[a]

	M062X/6-311+G** in THF			G3MP2B3 in THF		
Compound	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG
6+LiMe	0.0	0.0	0.0	0.0	0.0	0.0
6 complex	−1.4	−17.4	3.8	−1.7	−16.0	3.1
TS (**6**↔**11**)	7.8	−24.1	15.0	10.9	−18.6	16.5
TS (**6**↔**12**)	10.1	−25.4	17.7	14.4	−20.6	20.5
11+CH_4	−19.5	−5.0	−18.0	−18.4	−3.3	−17.4
12+CH_4	−22.6	−3.5	−21.6	−21.0	−2.9	−20.1

[a] Calculations use M062X/6-311+G** and G3MP2B3 with PCM/THF. Enthalpies and free energies (25 °C) are in kcal mol^{-1}, whereas entropies are in cal mol^{-1} K relative to **6**+LiMe.

generated by using MeLi base,[13] whereas Collum and co-workers used Me_2Li in their computational studies.[14] Interestingly, when the polarization continuum model (PCM, THF) was included, MeLi binding to the methoxy groups is enthalpically only slightly exothermic (M062X, −1.4 kcal mol^{-1}) compared to the gas phase (−17.6 kcal mol^{-1}). No MeLi binding to the chlorides could be found in solution whereas it does bind in the gas phase. Although the entropies are included as bimolecular values (**6** +MeLi), the true entropies will depend on the degree of solvation/aggregation, thus, the absolute barriers are not anticipated to be accurate but the selectivities and thermodynamics will be.

As shown in Table 5, selectivity favors attack at C3 (organolithium **11**) over C6 (organolithium **12**) by 2.7 (M062X) and 4.0 kcal mol^{-1} (G3MP2B3) indicative of high kinetic selectivity at C3. These two TSs and some of the critical bond parameters are shown in Figure 1 and for the DoM site, the TS is mostly C–H–C bond breaking/forming with the Li idling by interacting with the oxygen. If we assume that MeLi can reversibly bind to

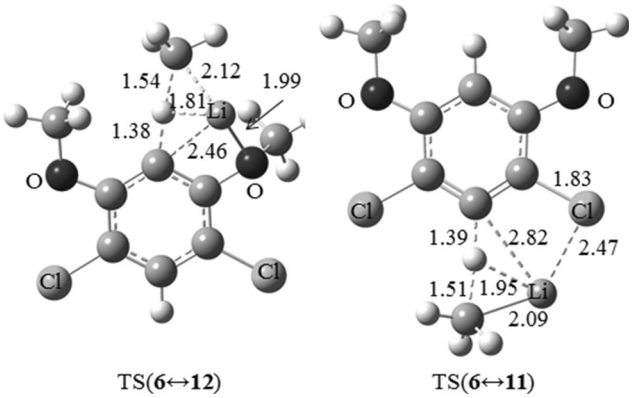


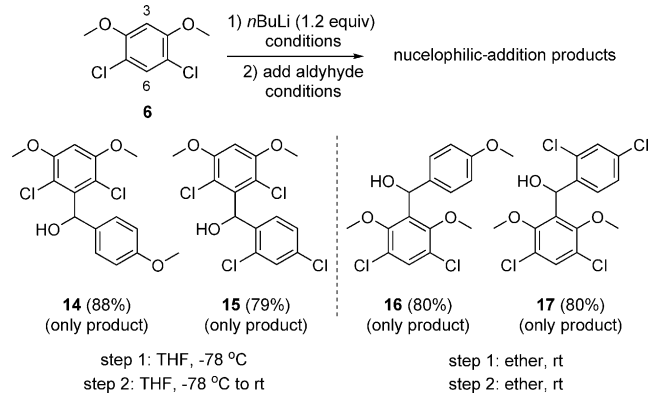
Figure 1. Important bond-length parameters in the two TSs defining the selectivity.

the oxygen atom in the complex, which is likely true due to the 11.2 (M062X) or 13.4 kcal mol^{-1} (G3MP2B3) difference between the TS and the complex, then the "templating" effect must be kinetic in nature and due to stabilization of the lithium by the oxygen in the transition state. Figure 1 supports this argument. From the kinetically preferred pathway, two isomers of **11** were computed, one with a distorted Li–O interaction, and one without this interaction with the former being lower in energy. However, the geometric isomer with the Li residing between the chlorides (**12**) is 3.6 (M062X) or 2.7 kcal mol^{-1} (G3MP2B3) more stable. Although no low-energy isomerization pathways could be discerned, the thermodynamically more stable product **12** is opposite of the kinetic product, as was demonstrated experimentally.

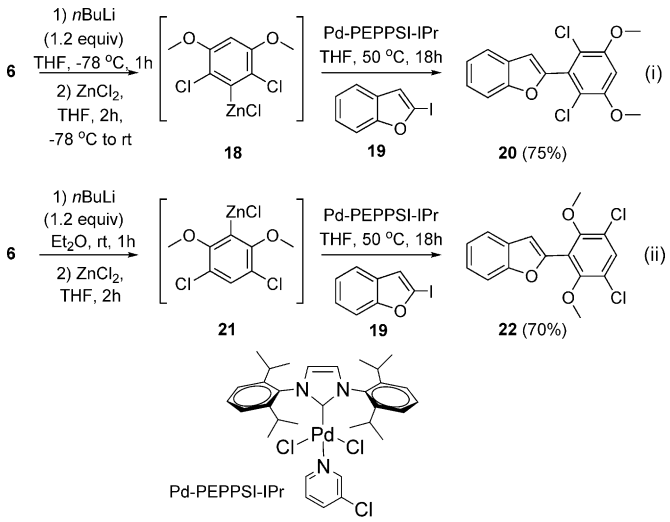
Synthetic utility

The remarkable ability to selectively form one anion in one solvent and another anion in a different one offers great opportunities for synthesis. Deprotonation of **6** in THF followed by addition of either electron-rich (**14**) or electron-poor (**15**) aldehydes gave selective attack at C6 (Scheme 5). Conversely, the same sequence conducted in Et_2O gave only the products of addition to C3 (i.e., **16** and **17**).

In another application, lithiation of **6** in THF followed by transmetalation with $ZnCl_2$ gave **18** that upon addition of Pd–PEPPSI-IPr and oxidative addition partner **19** led exclusively to the formation of **20** (Scheme 6 i).[15,16] Alternatively, DoM in Et_2O followed by transmetalation locks the organometallic at C3 (i.e., **21**), because the zinc derivative does not isomerize once the THF is added that is necessary for the Negishi coupling to give isomer **22** (Scheme 6 ii). Without this unique solvent feature, the direct cross-coupling of these two different sites on **6** would not be possible.



Scheme 5. Complementary regioselective nucleophilic additions to aldehydes in ether and THF.



Scheme 6. Complementary regioselective Negishi cross-coupling reaction of **6** in ether and THF.

Mechanistic considerations

At first glance, it would be tempting to suggest that the starting material (**6**) is lithiated at C3 by *n*BuLi that is templated strongly by the methoxy group(s) to produce **11**, which then deprotonates another molecule of starting material to produce **12** and in doing regenerates **6**. This would create a cycle that would systematically work its way until all of **6** is consumed and the lithiation mixture contains only **12**. The rates from Table 2 might suggest that this is possible, because DoM itself is comparatively slow, thus giving isomerization sufficient time to occur. However, the lithium/halogen exchange results in Table 3 suggest that such a straightforward mechanism is not the primary means by which **12** is formed. Here, **11** is formed instantaneously, and it is clear that complete isomerization takes more than 30 minutes. Thus, there has to be complete isomerization of **11** to **12** in THF that does not involve **6**, which does not happen in ether. This was further supported by the results shown in Scheme 3, in which **6** was fully converted to **11** in Et_2O, and it was not until the Et_2O was removed and the THF added that isomerization to **12** took place.

The unusually large selectivity observed when C3 is deuterated can be rationalized in terms of a rate-determining deprotonation of the complexed lithiated species in the DoM process. The unusually large deuterium isotope effect (DIE $>$ 99) observed is consistent with tunneling associated with cyclic (5 or 6 centered) transition states, in which small changes in geometry (narrow barriers) are involved in hydrogen atom- or proton-transfer reactions.[17] DIE values of 13000 (at $-150\,^{\circ}C$) have been reported for the isomerization of 2,4,6-tri-*tert*-butylphenyl to 3,5-di-*tert*-butylneophyl.[18] The DIE decreases with increasing temperatures (1400 and 80 at -100 and $-30\,^{\circ}C$, respectively) following nonlinear Arrhenius plots typical for those processes involving tunneling. Such temperature effects have also been observed in directed lithium deprotonation in the rearrangement of organic phosphates to phosphonates where a near-normal DIE of 6 was observed at $-50\,^{\circ}C$, which increased to ≥ 100 at $-78\,^{\circ}C$ in α-deprotonation.[19] The large KIEs observed in some of these transformations have led to the use of deuterium as a "protecting group" in directing regioselectivity, in which it is removed at a later stage.[8,20,21] In the current case, DoM occurs by rate-determining deprotonation at C3 via a 6-centered transition state (see Figure 1 TS **6**$\leftrightarrow$**11**). The corresponding activated complex for the C3-deuterated species lies 0.8 kcal mol^{-1} higher, which would predict a normal DIE of 7.9 at $-78\,^{\circ}C$ in contrast to the observed selectivity, in which the DIE must be at least 99 to account for it. Deprotonation at C6 does not involve DoM and the difference in activation energies between the C6 deuterated and protonated transition states of 0.9 kcal mol^{-1} leads to a normal predicted value of 10.3 at $-78\,^{\circ}C$, which is more consistent with the observed selectivity.

In summary, a remarkable solvent effect has led to the selective creation of two isomeric aryl lithium species during the DoM of 1,5-dichloro-2,4-dimethoxybenzene (**6**). Calculations have been used to determine that the C6-lithio species (**12**) is the thermodynamically more stable anion, and that templated deprotonation at C3 is the kinetically favored process leading to formation of **11**. Kinetic deprotonation at C3 by using *n*BuLi in THF can be deflected to C6 by placing a deuterium at C3, whereas in Et_2O, deprotonation (of D+) still occurs at C3.

These unique observations have been shown to have very useful applications in synthetic chemistry. Regioisomeric products can now be produced with full and absolute regioselectivity simply by changing the solvent from THF to Et_2O, thus eliminating the need for high-coordinating solvents, such as TMEDA or HMPA that are difficult to work with.[8] In fact, the addition of TMEDA to either the DoM reaction of **6** in THF or Et_2O did not alter the regioselectivity at all. The ability to readily reduce or further manipulate the chlorides (e.g., cross-couple) and methoxy groups will allow the preparation of diverse, highly substituted aryl compounds as single isomers, something that remains a formidable challenge in synthetic chemistry. This is especially important, because aromatic isomers are typically inseparable.

Acknowledgements

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Keywords: isotopes · Negishi coupling · PEPPSI · regioselectivity · solvent effects

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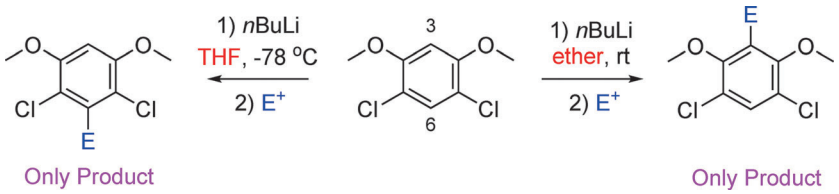

Simply changing the solvent from THF to diethyl ether dramatically alters the outcome of directed *ortho* metalation (DoM) of 1,5-dichloro-2,4-dimethoxybenzene. Kinetic deprotonation in both solvents occurs between the two methoxy groups; however, in THF, the 3-lithio derivative rearranges rapidly to the 6-lithio isomer, which is the thermodynamically more stable anion (see scheme).

Synthetic Methods

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Solvent Choice and Kinetic Isotope Effects (KIEs) Dramatically Alter Regioselectivity in the Directed *ortho* Metalation (DoM) of 1,5-Dichloro-2,4-dimethoxybenzene