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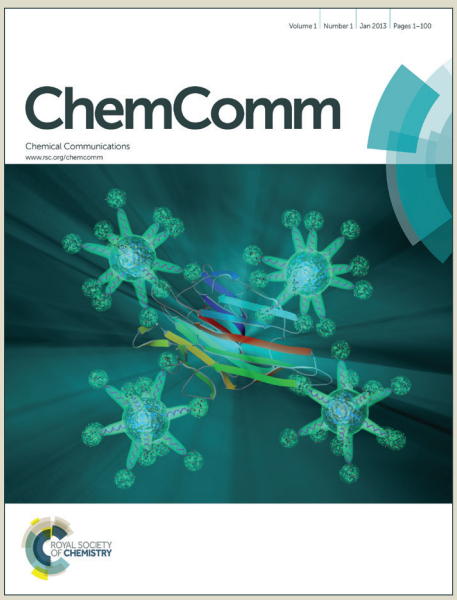

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Regioselective Desymmetrization of Diaryltetrahydrofurans via Directed *ortho*-Lithiation: An Unexpected Help from Green Chemistry†‡

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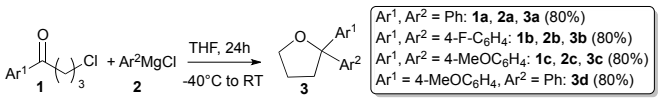
An efficient functionalization of diaryltetrahydrofurans via a regioselective THF-directed *ortho*-lithiation is first described. This reaction could be successfully carried out in cyclopentyl methyl ether as a "greener" alternative to Et_2O with better results in terms of yield and selectivity and, surprisingly, also in protic eutectic mixtures competitively with protonolysis.

Substituted tetrahydrofuran (THF) derivatives are important structural features commonly encountered in many synthetic and natural products with wide-ranging biological activity.[1] Their lack of reactivity, however, has discouraged their use as starting material in organic synthesis, which remains a challenging task. It's only recently that a few strategic THF ring elaborations have started to be documented; these include: direct functionalization reactions,[2] α-zincation,[3a] α-alumination,[3b] α-lithiation,[4] iron-catalysed ring-opening azidation and allylation,[5] and *N*-heterocyclic carbene-boranes promoted tetrahydrofuran nucleophilic substitutions.[6] As part of our program aimed at developing new aspects of reactivity of saturated oxygen-based heterocycles, we have recently discovered that an oxetane motif can act as an effective director of both α-lithiation[7] and *ortho*-lithiation.[8] Thus, we became interested in studying also the ability of the THF moiety in promoting the *ortho*-lithiation process.[9] Building on our recent findings, this paper describes the first successful use of tetrahydrofuran as an effective direct metalation group (DMG) in the regioselective desymmetrization/functionalization of diaryltetrahydrofurans. In the course of such an investigation it was found that (a) cyclopentil methyl ether proved to be a valid, greener alternative to Et_2O often providing better yields and higher selectivity, and (b) organolithium reactions could also be successfully carried out in protic eutectic mixtures as more environmentally friendly reaction media, thus unexpectedly opening up new avenues and possibilities for the organolithium field.

At the outset of our investigation, we selected 2,2-diphenyltetrahydrofuran **3a** as our model substrate taking into consideration the fact that a regioselective *ortho*-functionalization would create a chiral molecule via a desymmetrization reaction. Compound **3a** was straightforwardly prepared in 80% yield via an intramolecular basic cyclization by reacting a THF solution of the commercially available PhMgCl **2a** (3 equiv) with 4-chloro-1-phenylbutan-1-one **1a** (1 equiv) for 24h (Scheme 1). When an Et_2O solution of **3a** (1 equiv) was subjected to the conditions we used for the *ortho*-lithiation of aryloxetanes (*s*-BuLi (1.4 equiv), 0 °C, 10 min),[8] followed by quenching with MeI, we were pleased to find that the desired *ortho*-methylated adduct **4a** did indeed form in 65% yield (Table 1, entry 1), presumably through the putative *ortho*-lithiated intermediate **3a–Li**. Using a two-fold excess of the base led to an increase of the yield up to 80% (Table 1, entry 2), whereas longer lithiation time up to 60 min or the presence of a bidentate ligand such as tetramethylethylenediamine (TMEDA) (1.4 equiv)[10] resulted in isolation of **4a** in 75 and 50% yield, respectively (Table 1, entries 3,4).



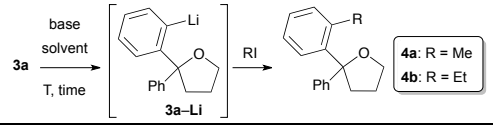
Scheme 1

The employment of temperatures as low as –78 and –20 °C as well as of different organolithium reagents such as *n*-BuLi and lithium diisopropylamide (LDA) failed to produce *ortho*-lithiation (Table 1, entries 5-8). Other solvents, such as THF and toluene, proved to be similarly ineffective (Table 1, entries 9,10). To our delight, the use of *t*-BuLi (1.9 equiv) as a base in Et_2O at 0 °C improved the conversion considerably allowing the recovery of **4a** in a nearly quantitative yield (> 98%) (Table 1, entry 11). Most probably, the stronger basicity of *t*-BuLi compensates the lower electron-donor ability of tetrahydrofuran in coordinating the lithium compared to that of an oxetane ring,[8] thereby promoting more efficiently the *ortho*-lithiation. Running the lithiation of **3a** with up to 4 equiv of *t*-BuLi in Et_2O, followed by quenching with MeI, however, did not provide any bis-methylated adduct, but only **4a** (> 98%) Thus, most probably, an *ortho*-dilithiated intermediate could not be formed.

With the optimized conditions in hand, a range of electrophiles was screened and results are reported in Table 2. As for heteroatom-based electrophiles, reaction of **3a–Li** with Bu_3SnCl, $PhSSO_2Ph$, and Ph_2PCl afforded the corresponding tin, sulphenyl, and phosphenyl derivatives **4c–e** in good to high yield (60–90%). Both chlorination and fluorination could also be successfully accomplished using hexachloroethane and *N*-fluorobenzenesulfonimide as Cl^+ and F^+ synthetic equivalents, thus leading to adducts **4f,g** in very good yield (85–90%). Trapping with both DMF and *N*,*N*-dimethylbenzamide delivered aldehyde **4h** and the aromatic ketone **4i**, respectively, both

in 90% yield. Remarcably, the reaction with 4-methylphenyl-1-isocyanate and ethyl 2-(bromomethyl)acrylate as more reactive electrophiles resulted in the formation of the amide **4j** and the allylated product **4k** bearing an ester moiety, both in good yield (70%). Reactions with carbonyl compounds proceeded equally well with enolizable aliphatic aldehydes. Indeed, **3a–Li** could be smoothly ortho functionalized with acetaldehyde and cyclohexanone affording the expected *ortho*-hydroxyalkylated derivatives **4l**,**m** in good yield (70%). No reaction, however, was detected with acetone (**4n**: 0%), and the addition to aromatic ketones (benzophenone) and aldehydes (4-chlorobenzaldehyde) gave a lower yielding reaction (**4o**,**p**: 40%).

Table 1 Optimization of the regioselective *ortho*-lithiation-alkylation of **3a** under different conditions.



Entry	Base (equiv)	Time (min)	T (°C)	Solvent	RI	**4a,b** yield (%)
1	*s*-BuLi (1.4)	10	0	Et_2O	MeI	**4a** (65)[a]
2	*s*-BuLi (2)	"	"	"	"	**4a** (80)[a]
3	"	60	"	"	"	**4a** (75)[a]
4	"[b]	10	"	"	"	**4a** (50)[a]
5	"	"	–78	"	"	**4a** (0)
6	"	"	–20	"	"	**4a** (<5)[c]
7	*n*-BuLi (2)	"	0	"	"	**4a** (0)
8	LDA (2)	"	"	"	"	"
9	*s*-BuLi (2)	"	"	THF	"	"
10	"	"	"	toluene	"	**4a** (20)[a]
11	*t*-BuLi (1.9)	"	"	Et_2O	"	**4a** (>98)[a]
12	"	"	"	CPME	"	"
13	"	"	"	"	EtI	**4b** (80)[a,d]

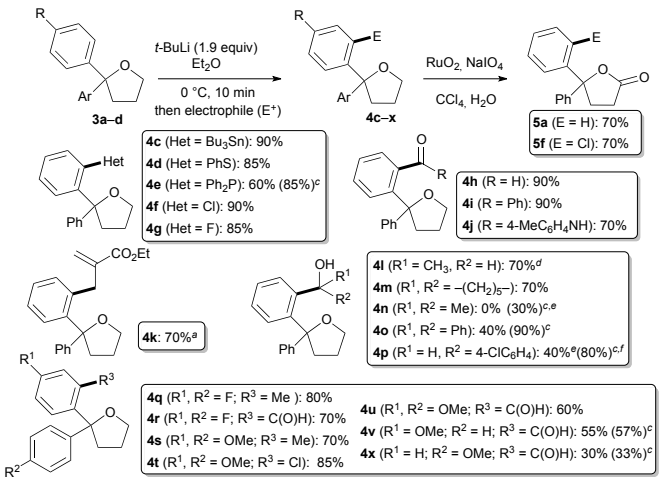
[a] Isolated yield after column chromatography. [b] 2 equiv of TMEDA. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] No reaction in Et_2O.

We also evaluated the sensitivity of the reaction to the substituents effects. To this end, symmetrically- and non-symmetrically-disubstituted diaryltetrahydrofurans **3b**–**d** with fluorine and methoxy groups were similarly prepared from the corresponding commercially available chloroketones **1b**,**c** and Grignard reagents **2a**–**c**, as outlined in Scheme 1. Once subjected to deprotonation-methylation, -chlorination, and -formylation sequences, all of them successfully furnished the *ortho*-substituted products **4q**–**u** in reasonable to very good yield (60–85%). In the case of the unsymmetrical THF derivative **3d**, a mixture of two separable regioisomers **4v**,**x** in 55 and 30% yield, respectively, was obtained upon deprotonation-formylation (Table 2). Anyway, the formation of adducts **4s**–**x** also testifies that the tetrahydrofuran ring is more effective at directing ortho lithiation than does a methoxy substituent. It is worth noting that the above diaryltetrahydrofurans can also be adequate precursors of the corresponding γ-butyrolactones, which are common structural motifs in many biologically active compounds and natural products. Indeed, compounds **3a**,**4f** consistently produced the corresponding lactones **5a,f** both in 70% yield (Table 2) once subjected to the system composed of catalytic ruthenium (IV) oxide and $NaIO_4$ in CCl_4/H_2O.

Environmentally friendly reaction media are continuously searched by the chemical industry with the aim of maximizing the sustainability and safety of chemical processes in particular during scale-up work. Cyclopentyl methyl ether (CPME), which can be produced directly from cyclopentene, has recently been promoted as a potential green alternative solvent for many organometallic reactions.[11] Thus, we wondered whether it could represent a valid alternative to Et_2O for carrying out the above *ortho*-lithiation reactions. We were delighted to find that subjecting **3a** to lithiation with *t*-BuLi (1.9 equiv, 0 °C) in CPME, followed by quenching with MeI, provided the expected adduct **4a** in almost quantitative yield (>98%) (Table 1, entry 12). We sought to capitalize on that by cross-checking results for some representative reactions run in CPME. Pleasingly, quenching **3a–Li** in CPME with both benzophenone and 4-chlorobenzaldehyde, which were shown to react sluggishly in Et_2O, furnished the corresponding hydroxyalkylated THF derivatives **4o**,**p** in 90% and 80% yield, respectively (Table 2). Similarly, in the case of chlorodiphenylphosphine, a better yield could be achieved for **4e** in CPME (85% vs 60% in Et_2O), whereas adducts **4v**,**x** were isolated in 57 and 33% yield, respectively, upon deprotonating **4d** in CPME followed by interception with DMF (Table 2).

Impressively, while no reaction was observed between **3a–Li** and EtI in Et_2O, the desired *ortho*-ethylated adduct **4b** formed in 80% yield in CPME (Table 1, entry 13). The reaction of **3a–Li** with acetone (6 equiv) in CPME took place as well, although the expected hydroxyalkylated compound **4n** formed in 30% yield only (Table 2). Most probably, in the case of acetone, under the above conditions, enolization still competes a lot with nucleophilic addition.

Table 2 Scope study for the directed *ortho*-lithiation of diaryltetrahydrofuran derivatives **3a**–**d**.[a,b]

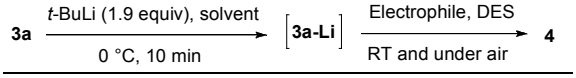


[a] Isolated yield after column chromatography. All reactions were conducted with 1 mmol of substrate in 0.5 M concentration. All products are racemic mixtures. [b] Both compounds **4v**,**x** derive from the reaction of **3d**. [c] Reaction run in CPME (0.5 M). [d] Isolated as a mixture of two separable diastereomers (60:40). [e] This yield also refers to reactions in which an Et_2O solution was reacted with an acetone-water mixture (6 equiv each) or with neat acetone (6 equiv). [f] Isolated as a mixture of two inseparable diastereomers (60:40).

A recent paper by Madsen and Holm has shown that in the presence of protic reagents such as water the rate of carbonyl addition from highly reactive Grignard reagents is comparable to that of protonation by the same reagent.[12] In the case of the more polar and basic organolithium reagents, one would expect that protonation occurs almost instantaneously. However, once an Et_2O solution of **3a–Li** (0.45 M) was spread out over an acetone-water mixture (6 equiv each) at room temperature it was somewhat surprising to find that the desired adduct **4n** could still be recovered in 30% yield (Table 2). In a subsequent experiment in which the above ethereal solution of **3a–Li** was added to acetone alone (6 equiv) (neat conditions) product **4n** again formed in 30% yield (Table 2). This result implies that the formation of **4n** is unrelated to any "rate acceleration" promoted by water; instead, the key to success may be the

"inverse addition".[13] It is, however, intriguing the apparent role as a "spectator" played by water in the above addition.[14] A perusal of the literature revealed that water can act as a polar ligand towards lithium[15] successfully competing also with TMEDA.[15b] Thus, to further assess the potential impact of protic solvents on organolithium chemistry, we turned our attention to the so-called deep eutectic solvents (DESs) which were introduced by Abbott and co-workers in 2003[16a] and rapidly emerged as a new generation of promising green media. They are the result of the right combination of a hydrogen-bond donor and a hydrogen-bond acceptor that form an eutectic with a melting point much lower than either of the individual components, and are known to exhibit interesting and unusual solvent properties.[16b,c]

Table 3 Regioselective preparation of intermediate **3a–Li** and quenching with electrophiles in ChCl-containing DES mixtures.



Entry	Solvent	DES[a]	Electrophile	4 yield (%)[b]
1	Et_2O	ChCl/Gly (1:2)	Acetone	**4n** (40)
2	CPME	"	Benzophenone	**4o** (75)
3	"	ChCl/urea (1:2)	"	"
4	"	ChCl/H_2O (1:2)	"	**4o** (33)
5	"	ChCl/urea (1:2)	Ph_2PCl	**4e** (75)
6	"	ChCl/Gly (1:2)	DMF	**4h** (90)[c,d]

[a] DES: 2 g per 1 mmol of **3a**. [b] Isolated yield after column chromatography, the remaining being starting material only. [c] *t*-BuLi (1.9 equiv, 1.7 M) was added to a solution of **3a** in DES . [d] Reaction time 1 min.

Once an Et_2O solution of **3a–Li** (1.9 equiv, 0.5 M) was added to acetone (6 equiv) in a choline chloride (ChCl)-glycerol (Gly) (1:2) eutectic mixture at *room temperature (RT) and under air*, adduct **4n** could now be recovered with a yield of 40% (Table 3, entry 1). Similarly, the addition reaction of a CPME solution of **3a–Li** (1.9 equiv, 0.5 M) to benzophenone (2 equiv) as the electrophile run either in a ChCl/Gly (1:2) or in a ChCl/urea (1:2) DES mixture smoothly afforded the desired *ortho*-hydroxyalkylated product **4o** in both cases in 75% yield (Table 3, entries 2,3). A decrease in selectivity, however, was observed when the addition to benzophenone was carried out in ChCl/H_2O (1:2) DES, the yield in **4o** being 33% only (Table 3, entry 4). Chlorodiphenylphosphine (2 equiv) also readily underwent nucleophilic substitution in ChCl/urea (1:2) to give the corresponding adduct **4e** in 75% yield (Table 3, entry 5). Finally, we also investigated the formation of anion **3a–Li** *directly* in the protic DES mixture *in the absence of the electrophile*. To this end, *t*-BuLi (1.9 equiv, 1.7 M) was added at *0 °C and under air* to a solution of **3a** (1 mmol previously solubilized in 2 mL of CPME) in the ChCl/Gly (1:2) eutectic mixture (2 g) under vigorous stirring. After 1 min reaction time, the reaction mixture was quenched with neat DMF (2 equiv) astonishingly affording the expected adduct **4h** in 90% yield (Table 3, entry 6). It follows from the above that the formation of intermediate **3a–Li** from *t*-BuLi, surprisingly, takes place competitively with the protonolysis of the latter.

In summary, we have reported the first direct regioselective *ortho*-lithiation/functionalization of diaryltetrahydrofurans in which the THF moiety acts as an effective DMG. *Ortho*-lithiation was found to proceed smoothly using *t*-BuLi as the base at 0 °C both in Et_2O and in CPME, the latter often providing better yields and selectivity compared to Et_2O. In addition, we noticed that both generation of the *ortho*-lithiated derivative **3a-Li** and its trapping reactions with electrophiles could also be fruitfully performed at 0 °C or RT and under open air conditions in eutectic mixtures of ChCl and donor molecules such as glycerol and urea competitively with protonolysis. Our next aim is to set up an enantioselective desymmetrization of diaryltetrahydrofurans in the presence of chiral ligands as well as to deeply investigate the scope of protic DES mixtures as new eco-friendly reaction media for organolithium reactions.

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Notes and references

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† This communication is dedicated to Professor R. J. K. Taylor on the occasion of his 65th birthday.

‡ Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data, and copies of $^1H/^{13}C$ NMR spectra of compounds **3b–d**, **4a–x**, and **5f**. See DOI: 10.1039/c000000x/

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