ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 8655

Received 28th April 2014,
Accepted 20th May 2014

DOI: 10.1039/c4cc03149k

www.rsc.org/chemcomm

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 can 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 a 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-borane 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 also studying the ability of the THF moiety to promote an *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 our investigation it was found that (a) cyclopentyl 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 24 h (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 a longer lithiation time of 60 min, or the presence of a bidentate ligand such as tetramethylethylenediamine (TMEDA) (2 equiv.)[10] resulted in the isolation of **4a** in 75 and 50% yields, respectively (Table 1, entries 3 and 4).

The employment of temperatures as low as −78 and −20 °C, as well as 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 and 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 for the lower electron-donor ability of tetrahydrofuran in coordinating the lithium compared to that of an oxetane ring,[8] thereby promoting more efficiently the

Scheme 1

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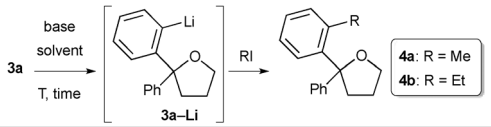
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and copies of the $^1H/^{13}C$ NMR spectra of compounds **3b–d**, **4a–x**, and **5f**. See DOI: 10.1039/c4cc03149k

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

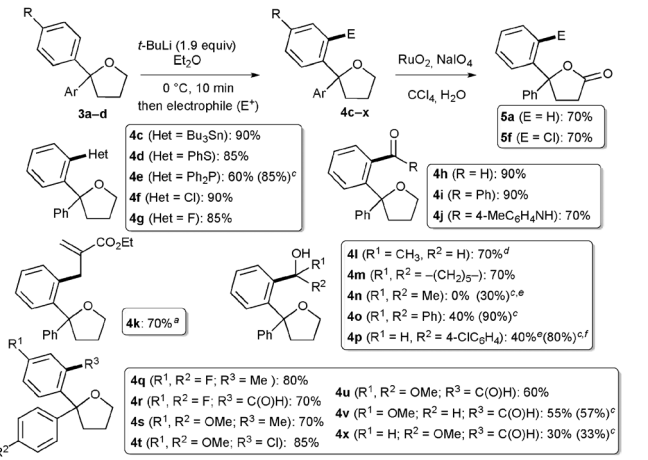
Table 1 Optimization of the regioselective *ortho*-lithiation–alkylation of **3a** under different conditions



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

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** and **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).

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 the results are reported in Table 2. As for heteroatom-based electrophiles, the 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 yields (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** and **g** in very good yields (85–90%). Trapping with both DMF and *N*,*N*-dimethylbenzamide delivered aldehyde **4h** and the aromatic ketone **4i**, respectively, both in 90% yield. Remarkably, the reactions 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** and **m** in good yield (70%). No reaction, however, was detected with acetone (**4n**: 0%), and the addition to an aromatic ketone (benzophenone) and aldehyde (4-chlorobenzaldehyde) gave lower yielding reactions (**4o** and **p**: 40%).

We also evaluated the effects of substituents on the sensitivity of the reaction. 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** and **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 yields (60–85%). In the case of the unsymmetrical THF derivative **3d**, a mixture of two separable regioisomers **4v** and **x** in 55 and 30% yields, respectively, was obtained upon deprotonation–formylation (Table 2). The formation of adducts **4s–x** also indicates that the tetrahydrofuran ring is more effective at directing *ortho*-lithiation than 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** and **4f** consistently produced the corresponding lactones **5a** and **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 being searched for 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 an 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

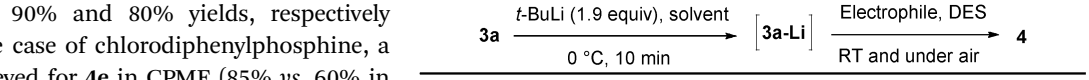
and 4-chlorobenzaldehyde, which were shown to react sluggishly in Et_2O, furnished the corresponding hydroxyalkylated THF derivatives **4o** and **p** in 90% and 80% yields, respectively (Table 2). Similarly, in the case of chlorodiphenylphosphine, a better yield could be achieved for **4e** in CPME (85% *vs.* 60% in Et_2O), whereas adducts **4v** and **x** were isolated in 57 and 33% yields, respectively, upon deprotonating **3d** 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 the nucleophilic addition.

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 reagents.[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 added 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] However, the apparent role as a ''spectator'' played by water in the above addition is intriguing.[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 a 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]

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 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 ChCl–urea (1 : 2) DES mixture, smoothly afforded the desired *ortho*-hydroxyalkylated product **4o** in both cases in 75% yield (Table 3, entries 2 and 3). A decrease in selectivity, however, was observed when the addition to benzophenone was carried out in a ChCl–H_2O (1 : 2) DES, the yield of **4o** being only 33% (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 an 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.), remarkably 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.

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	ChCl–Gly (1 : 2)	Benzophenone	**4o** (75)
3	CPME	ChCl–urea (1 : 2)	Benzophenone	**4o** (75)
4	CPME	ChCl–H_2O (1 : 2)	Benzophenone	**4o** (33)
5	CPME	ChCl–urea (1 : 2)	Ph_2PCl	**4e** (75)
6	CPME	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.

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 the generation of *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 a new eco-friendly reaction media for organolithium reactions.

This work was financially supported by the Interuniversities Consortium C.I.N.M.P.I.S. We also thank Professor Saverio Florio and Professor Dietmar Stalke for valuable discussions.

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