**Lateral lithiation in deep eutectic solvents: regioselective functionalization of substituted toluene derivatives**



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# Lateral Lithiation in Deep Eutectic Solvents: Regioselective Functionalization of Substituted Toluene Derivatives

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**Abstract. The heteroatom-directed lateral lithiation of functionalized toluenes in a choline chloride-based eutectic mixture is reported. The metalations proceed within ultrafast reaction times, with a broad substrate and electrophile scope. The directing groups provide a rapid and high regioselective access to functionalized aromatic derivatives of remarkable synthetic value.**

The directed *ortho*-metalation (D*o*M) and the lateral metalation (LM) of aromatic compounds have assumed a pivotal role in synthesis since the seminal report by Gilman and Morton.[1] Nowadays these strategies represent a powerful and well-consolidated methodology for the construction of polysubstituted aromatics and heteroaromatics, which have overtaken the classical electrophilic aromatic substitution for the assembly of regiospecifically substituted aromatic rings. The ongoing development of novel metalation reagents for the *ortho*-aryl deprotonation (D*o*M), which has been extensively reviewed in the literature, clearly illustrates the continued importance of this class of transformation.[2] In strong relationship with the D*o*M strategies, of equal synthetic utility is the development of methodologies for the lateral metalation of benzylic alkyl groups promoted by heteroatom-containing substituents (directing groups, DGs).[3, 4] Overall, extensive investigations have clearly established that, for either class of reaction, amides, carbonates and oxazolines are the most powerful directors.[2b-c, 2e] Due to the obvious competition with the *ortho*-deprotonation process resulting from the presence of similar DGs, LM often suffers of cumbersome regioselectivity issues. Hence, of particular interest is the development of synthetic methods for the selective benzylic metalation of alkyl-substituted aromatic compounds minimizing the competitive D*o*M pathway (Scheme 1, A).[5] Organolithium reagents are elective organometallic species for promoting the lateral lithiation (LL) of substituted toluenes.[2d, 3-4] However, owing to their well-known air and moisture sensitivity, strictly controlled experimental conditions are usually required to avoid both the degradation of intermediate lithiated species and undesired side reactions.[6] Thus, the identification of new synthetic strategies involving polar organometallic reagents under aerobic and protic conditions nowadays represents a fascinating and ultimate challenge in this area. Additionally, the transition to synthetic methodologies where traditional solvents are replaced by water or low-impact alternatives strongly concurs to the goal of attaining sustainability.[7] For this purpose, Deep Eutectic Solvents (DESs) represent a novel and promising class of unconventional, green solvents, that can potentially replace the classical petroleum-derived volatile organic compounds, VOCs.[8] In this context, the chemistry of polar organometallic compounds has recently experienced a deep revolution by virtue of the independent investigations by Hevia, García-Álvarez and Capriati on the reactivity of Grignard and organolithium reagents in the alkylation/arylation of ketones, imines and nitriles, at room temperature (RT), under air, and in DESs or glycerol (Gly) or water.[9] Furthermore, regio- and chemoselective D*o*M reactions using cyclopentyl methyl ether (CPME) and choline chloride (ChCl)-based eutectic mixtures as solvents under air have been recently reported,[10] while to the best of our knowledge only one example of regioselective lateral lithiation of diaryl-THF derivatives has been described hitherto in protic media under hydrous conditions (Scheme 1, B).[11] Building on our long-standing interest in polar organometallic chemistry[12] and our recent findings in using heterogeneous bio-based solvent mixtures for the chemoselective D*o*M of hindered benzamides,[10b] we now report a systematic study on the usefulness of DESs as sustainable media for promoting the regioselective lateral lithiation of substituted toluene derivatives (Scheme 1, C). Notable features of our report include a) the use of environmentally friendly conditions (absence of VOCs and open-air conditions), b) screening and identification of the most

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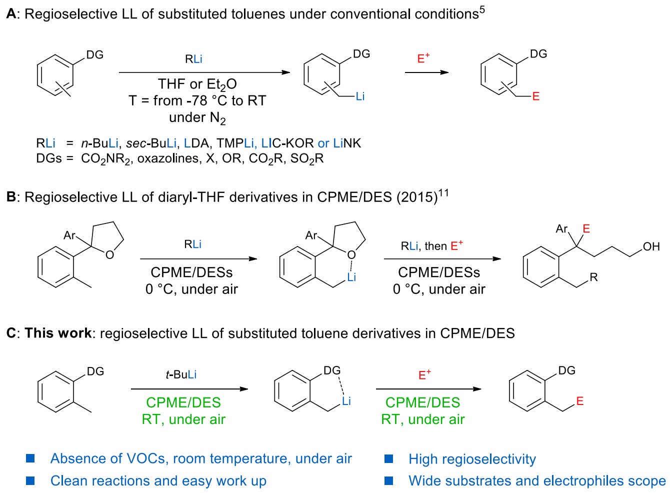
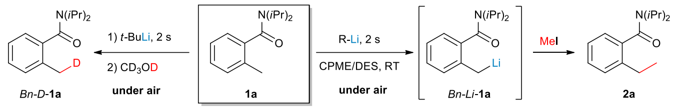



**Scheme 1**. State-of-the-art of the heteroatom-directed lateral lithiation of alkyl-substituted aromatic compounds.

suitable directing groups for regioselective LL, c) clean reactions and easy work-up procedures and d) wide substrates and electrophiles scope.

We started our investigations using the *N*,*N*-diisopropyl-2-methylbenzamide **1a** as a model substrate, since a) we have already demonstrated that this directing group can efficiently promote the *ortho*-lithiation in CPME/DESs heterogeneous mixtures[10b] and b) the LL of tertiary *o*-alkylbenzamides is generally performed using LDA[13] or *sec*-BuLi/TMEDA[14] in VOCs at low temperatures in order to avoid self-condensation of the lithiated species. Based on our previous findings,[10b] a vigorously stirred suspension of amide **1a** (0.2 mmol, 1 M in CPME)[15] in a ChCl/Gly (1:2 mol/mol) eutectic mixture was treated with a commercial 1.7 M pentane solution of *t*-BuLi (2 eq.) at RT under air. Instantaneous quench of the reaction mixture with MeI (5 eq.) afforded the corresponding *N*,*N*-diisopropyl-2-ethylbenzamide **2a** in 62% yield (Table 1, entry 1) alongside with 6% of α,α-dimethylated byproduct (see ESI for details). Notably, in the absence of CPME as an additive no lithiation occurred and the starting material **1a** was quantitatively recovered after workup (Table 1, entry 2). The regioselectivity of the metalation was assessed by $^1H$ and $^2H$ NMR analyses of the products arising from the deuteration of *Bn-Li*-**1a** with $CD_3OD$. Under these conditions the reaction gave almost exclusively benzylic deuterated product *Bn-D*-**1a** (91% D) with no detectable incorporation of D in the *ortho*-position (see ESI).[16] Efforts were made to further improve the conversion of the starting material and suppress the formation of the undesired bis-functionalized byproduct. No improvements were observed when the reaction was performed at 0 °C (Table 1, entry 3) or switching ChCl/urea (1:2 mol/mol) for ChCl/Gly (Table 1, entry 4), whereas the use of water as the hydrogen bond donor was ineffective (Table 1, entry 5). Lowering the equivalents of electrophile (Table 1, entries 6) led to a decrease of conversion, while reducing the amount of lithiating agent to 1.5 eq. gave the best results in terms of yield and suppression of byproduct, as confirmed by $^1H$ and $^2H$ NMR analysis of the corresponding deuterated product *Bn-D*-**1a** (Table 1, entries 9-10 and Figure S12, ESI).

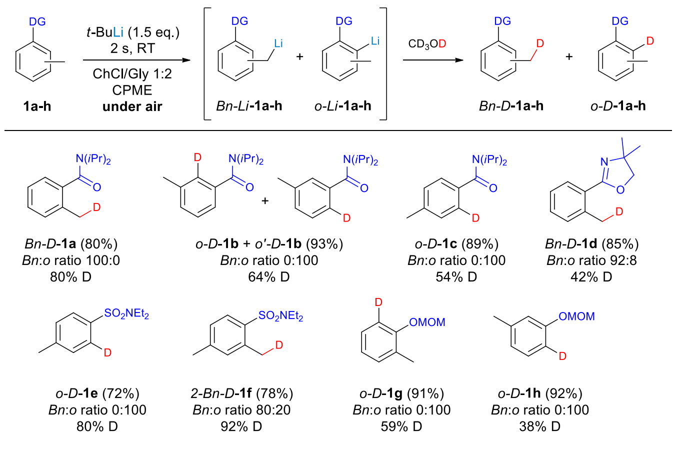
**Table 1**. Metalation reaction of *N*,*N*-diisopropyl-2-methylbenzamide **1a** under different conditions.[a]



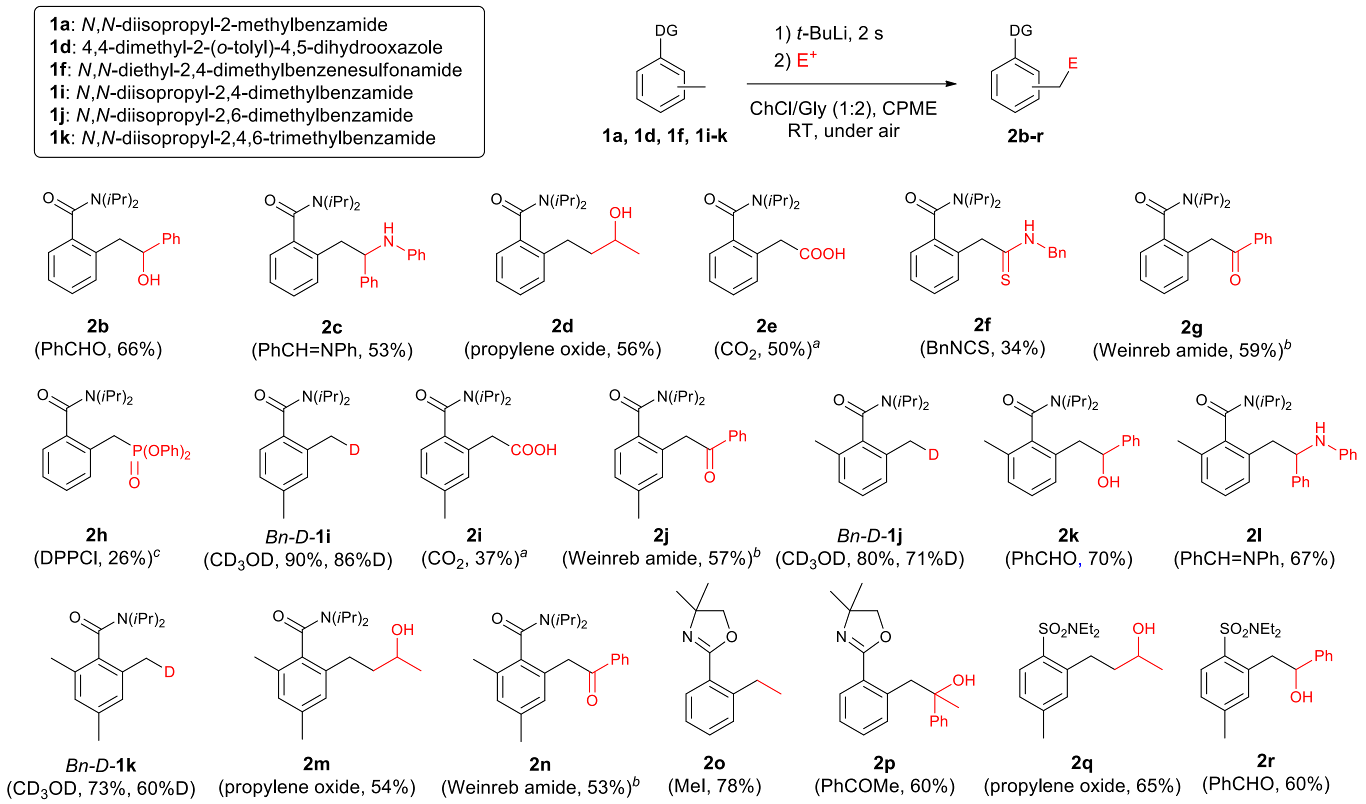

| Entry | DES | R-Li (eq.) | E+ (eq.) | Product (yield %)[b] |
|---|---|---|---|---|
| *1* | ChCl/Gly | *t*-Bu (2) | MeI (5) | **2a** (62) |
| *2* | ChCl/Gly[c] | *t*-Bu (2) | MeI (5) | - |
| *3* | ChCl/Gly[d] | *t*-Bu (2) | MeI (5) | **2a** (52) |
| *4* | ChCl/urea | *t*-Bu (2) | MeI (5) | **2a** (59) |
| *5* | ChCl/$H_2O$ | *t*-Bu (2) | MeI (5) | - |
| *6* | ChCl/Gly | *t*-Bu (2) | MeI (3) | **2a** (41) |
| *7* | ChCl/Gly | *t*-Bu (1) | MeI (5) | **2a** (50) |
| *8* | ChCl/Gly | *t*-Bu (1.2) | MeI (5) | **2a** (58) |
| *9* | ChCl/Gly | *t*-Bu (1.5) | MeI (5) | **2a** (70) |
| *10* | ChCl/Gly | *t*-Bu (1.5) | $CD_3OD$ (5) | *Bn-D*-**1a**[e] |
| *11* | ChCl/Gly | *n*-Bu (1.5) | MeI (5) | **2a** (26) |
| *12* | ChCl/Gly | *s*-Bu (1.5) | MeI (5) | **2a** (38) |

[a] Reaction conditions: 1.0 g DES per 0.2 mmol of **1a**, CPME (0.2 mL); DES: ChCl/Gly (1:2 mol $mol^{-1}$); ChCl/urea (1:2 mol $mol^{-1}$); ChCl/$H_2O$ (1:2 mol $mol^{-1}$). [b] Determined by $^1H$ NMR using $CH_3NO_2$ as the internal standard. [c] No CPME was added. [d] T = 0 °C. [e] *Bn-D*-**1a**: 80% isolated yield, 80% D incorporation.

Notably, other organolithiums such as *n*-BuLi and *s*-BuLi were considerably less effective in promoting the lateral metalation under these conditions (Table 1, entries 11-12). The half-life of *Bn-Li*-**1a** in the above protic medium was then evaluated by quenching multiple reaction samples with MeI at different times. The estimated half-life for *Bn-Li*-**1a** from the first-order plot obtained is 6.57 s, which is consistent with the *ortho*-Li *N*,*N*-diisopropylbenzamide[10b] in the same heterogeneous solvent system (see ESI for details). The selectivity of the lithiation reaction was then investigated for a series of *ortho*-, *meta*- and *para*-substituted toluenes bearing different DGs (Scheme 2). The substrates were treated with *t*-BuLi (1.5 equiv.) in CPME/DES (ChCl/Gly 1:2) mixture at RT under air followed by




**Scheme 2**. Metalation reaction of substituted toluenes **1a-h** using *t*-BuLi in CPME/DES at RT under air. Reaction conditions: **1a-h** (0.2 mmol), CPME (0.2 mL), DES (1.0 g), $CD_3OD$ (5 eq.). DES: ChCl/Gly (1:2 mol $mol^{-1}$). Ratios and D incorporation are based on $^1H$ NMR integration and confirmed with $^2H$ NMR. Yields in brackets refer to products isolated after flash column chromatography.




**Scheme 3**. Scope of the lateral lithiation reaction of substituted toluenes **1a**, **1d**, **1f**, and **1i-k** in CPME/DES (ChCl/Gly 1:2 mol mol$^{-1}$) mixture. Reaction conditions: substrate (0.2 mmol), *t*-BuLi (1.7 M in pentane, 0.4 mmol), CPME (0.2 mL), DES (1.0 g), electrophile (5 eq.). Reported yields refer to products isolated after flash column chromatography. [a] $CO_2$ was bubbled for 15 s. [b] Weinreb amide: *N*-methoxy-*N*-methylbenzamide. [c] DPPCl: diphenyl phosphoryl chloride.

quenching with $CD_3OD$ after 2 s, and analyzed by $^1H$ and $^2H$ NMR (Figure S17, ESI). The strongest DG of the series, namely the tertiary amide group, efficiently promoted the sole *ortho*-lithiation of both *meta*- and *para*-substituted derivatives **1b** and **1c** under these conditions (Scheme 2, *o-D*-**1b** and *o-D*-**1c**). These results are coherent with those reported for the same reactions run under conventional metalation conditions,[17] as a matter of fact regioselective lateral lithiation of **1c** entails the use of hindered lithium amides[2a, 5e] while the benzylic lithiation of **1b** has never been described so far. On the other hand, the oxazolinyl moiety is a versatile coordinating DG able to efficiently promote both DoM of benzene derivatives and the lithiation of tolyl methyl groups.[18] Pleasingly, treatment of the *ortho*-tolyl oxazoline **1d** with *t*-BuLi at RT under air gave almost complete regioselective benzylic metalation (Scheme 2, *Bn-D*-**1d**) with an overall 42% D incorporation. Tertiary sulfonamides also represent powerful DGs for DoM and LL processes. Under these conditions, lithiation of the *para*-methyl tertiary sulfonamide **1e** afforded the sole kinetic *ortho*-lithiation *o-D*-**1e** product,[19] while treatment of the 2,4-dimethyl derivative **1f** gave high D incorporation in the benzylic position proximal to the DG together with a 20% D incorporation in the *ortho*-position (Scheme 2). The weaker methoxymethoxy (OMOM) DG, which offers a remarkable regiocontrol of the lithiation reaction under conventional conditions with high selectivity for DoM over LL,[20] was finally investigated. Unsurprisingly, full *ortho*-selectivity was observed for the lithiation/deuteration of both *ortho*- (**1g**) and *meta*-OMOM (**1h**) substituted toluenes in CPME/DES, however with low D incorporation (Scheme 2, *o-D*-**1g** and *o-D*-**1h**).

Based on data reported in Scheme 2, derivatives of substrates **1a**, **1d** and **1f** were than selected to evaluate the generality of this transformation (Scheme 3). Carbonyl electrophiles such as aldehydes and imines reacted smoothly with anion *Bn-Li*-**1a**, thereby providing the expected lateral functionalized adducts **2b** and **2c** in good yields (66% and 53% respectively). The benzylic anion *Bn-Li*-**1a** promoted the regioselective ring opening of 1,2-propylene oxide affording the corresponding homologation product **2d** in 56% yield. Acylation of *Bn-Li*-**1a** successfully proceeded using $CO_2$ and the aromatic Weinreb amide (*N*-methoxy-*N*-methylbenzamide) as electrophiles, affording the corresponding substituted phenylacetic acid **2e** and ketone **2g** in 50% and 59% yield respectively (Scheme 3).[21] The quenching reaction of *Bn-Li*-**1a** with base-sensitive functional groups (e.g. isothiocyanates and diphenyl phosphoryl chloride) was less favorable and furnished the thioamide **2f** and the phosphonate derivative **2h** in lower yields (34% and 26%). However, attempted halogenation of *Bn-Li*-**1a** using chlorinating, brominating or iodinating agents resulted in low conversions and only the corresponding homocoupling products were detected in the reaction mixture.[12e] The directing ability of the tertiary amide group was then exploited for the regioselective lateral lithiation of substituted xylenes **1i-k**. Deuterium labelling experiments (metalation followed by deuteration of *Bn-Li*-**1i-k**) showed high benzylic selectivity with no detectable D incorporation at the para- position for 2,4-dimethyl and mesityl derivatives **1i** and **1k**, while notably no bis-deuterated products were observed upon lithiation of substrate **1j**. Hence, electrophilic quench of *Bn-Li*-**1i-k** with aldehydes, imines, amides and epoxides provided the corresponding products **2j-n** with good overall yields (53-70%) (Scheme 3). On the other hand, acylation of *Bn-Li*-**1i** with $CO_2$ proceeded with lower yield, affording the substituted phenylacetic acid **2i** in 37% yield. The scope of this transformation was also extended to the other previously investigated DGs, as such *o*-tolyl oxazoline **1d** and *o*,*p*-dimethyl sulfonamide **1f**. The lithiation efficiently occurred proximal to the DGs moiety and led to the formation of adducts **2o-r** in good yields (60-78%) upon quenching of the corresponding *Bn-Li*-**1d** and *Bn-Li*-**1f** anions with alkylating agents, such as iodomethane and propylene oxide, and carbonyl electrophiles (Scheme 3).

In summary, we have reported the directed lateral lithiation on functionalized toluene derivatives under air, at RT, within a reaction time of 2 s and using environmentally friendly deep eutectic mixtures in combination with cyclopentyl methyl ether (CPME). The reaction conditions are exceedingly mild, reaction times very fast and work-up straightforward. The most widely used DGs in *ortho*- and lateral lithiation reactions (tertiary amides, sulfonamides and oxazolines) preserve their relative directing abilities and efficiently promote the LL under these conditions. The scope has been extended to various substrates and electrophiles, thus providing rapid access to functionalized aromatic derivatives suitable for further synthetic transformations. Taken together our results represent an important advance in the chemistry of polar organometallic reagents in unconventional protic media as an alternative and green paradigm to traditional anhydrous, low temperatures and inert conditions. We expect that in the near future this approach will be expanded to other broadly used organometallic mediated transformations, thus paving the way to more general applications of green chemistry principles.

## Conflicts of interest

There are no conflicts to declare.

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