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Directed *ortho*-Metalation–Nucleophilic Acyl Substitution Strategies in Deep Eutectic Solvents: The Organolithium Base Dictates the Chemoselectivity

Simone Ghinato,^a Giuseppe Dilauro,^b Filippo Maria Perna,^b Vito Capriati,^{b,*} Marco Blangetti^{a,*} and Cristina Prandi^{a,*}

^a*Dipartimento di Chimica, Università di Torino, via P. Giuria 7, 10127 Torino, Italy*

^b*Dipartimento di Farmacia, Scienze del Farmaco, Università di Bari “A. Moro”, Consorzio C.I.N.M.P.I.S. Via E. Orabona 4, I-70125 Bari (Italy)*

Corresponding authors: Cristina Prandi, Marco Blangetti, Vito Capriati

Phone: +39-0116707643; +39-0116708033.

E-mail address: cristina.prandi@unito.it; marco.blangetti@unito.it, vito.capriati@uniba.it

Abstract. We report a general and rapid chemoselective functionalization of aromatic carboxylic acid amides with organolithium reagents by using Deep Eutectic Solvents (DESs) as environmentally friendly reaction media. Directed *ortho* metalation or nucleophilic acyl substitution processes can be selectively privileged at room temperature in air depending on the nature of the organolithium species. One-pot sequential *ortho*-lithiation/Suzuki-Miyaura cross-couplings have also been demonstrated for the first time in DESs. This opens up new synthetic opportunities in terms of efficiency and environmental sustainability.

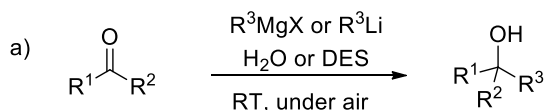
Amides are excellent starting materials and intermediates for organic synthesis due to their easy availability and preparation,^[1] and versatile reactivity.^[2] The reaction of highly reactive s-block organometallic compounds with aromatic amides may lead to two results: directed *ortho* metalation (DoM) with aromatic C–H functionalisation or nucleophilic acyl substitution (S_NAc). Among direct metalation groups (DMGs), the pioneering work of Beak and co-workers in this area established that tertiary benzamides can be more effective

than any other non-amide units in directing lithiation to an adjacent position provided that a bulky base (e.g. *sec*-BuLi) jointly with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as the complexing agent are used at $-78\text{ }^{\circ}\text{C}$ in THF. The choice of reactants and metalation conditions is, indeed, crucial to avoid the competing nucleophilic substitution.^[3] On the other hand, the direct, selective acylation of the above organometallics is notoriously complicated by the over-addition of these reagents to the product ketones leading to the formation of tertiary alcohols. One general solution to favor acyl-transfer reactions is to improve the stability of the transient tetrahedral intermediate, thereby avoiding its collapse to the ketone during the reaction.^[4] In this context, successful strategies have included the use of (a) Weinreb amides with chelating functional groups,^[5] (b) *N*-acylpyrroles,^[6] (c) chemoselective methods based on an activation/addition sequence on secondary amides,^[7] and (d) the use of *N*-acylazetidines as twisted amides.^[8] The use of non-conventional solvents as a method of controlling the $\text{S}_{\text{N}}\text{Ac}$ process is under-developed. Increasing environmental awareness has pressured companies to become more proactive in addressing public concerns related to the development of cleaner methods of chemical production and to drive the field of synthetic chemistry toward more green practices.^[9] The use of renewable feedstocks, which is one of the 12 principles of Green Chemistry, is seen by many as an important strategy towards sustainable development.^[10] The ability to telescope multiple bond-forming events in a one-pot process is another strategy to reduce the amount of solvent used in a synthetic sequence, and minimize waste production. From these perspectives, Deep Eutectic Solvents (DESs, easily obtainable by mixing and gently warming two or three safe and inexpensive components that can undergo self-association) represent a novel and promising class of unconventional, green solvents, that can potentially replace the classical petroleum-derived volatile organic compounds (VOCs). Common mixtures derive from a quaternary ammonium salts (e.g., choline chloride, ChCl) and a neutral hydrogen-bond donor (HBD) [e.g., glycerol (Gly), urea, natural carboxylic acids, amino acids], and thus they are exceptionally high biodegradable with toxicities that are non-existent or very low.^[11] Recent independent investigations by Hevia, García-Álvarez and Capriati on the reactivity of Grignard and organolithium reagents in protic, biorenewable media and under hydrous conditions (often considered the natural foes of these organometallic reagents) have established a step change in the way that the chemistry of these commodity reagents can be carried out using environmentally friendly conditions: alkylation/arylation of ketones, imines and nitriles, at room temperature (RT), under air, and in DESs or glycerol or water, have provided tertiary alcohols, amines, ketones and carbinamines in very good

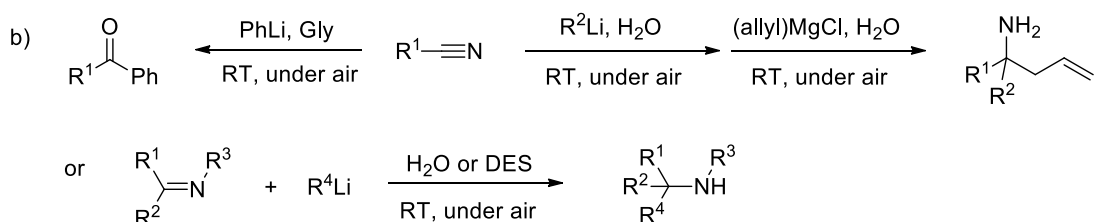
yields and competitively with protonolysis (Scheme 1a,b).^[12] A THF-directed *ortho*-lithiation and lateral lithiation in ChCl-based eutectic mixtures in the presence of cyclopentyl methyl ether (CPME) has also successfully granted access, under open air conditions and at RT, to functionalized diaryltetrahydrofurans and primary alcohols, respectively.^[13]

Previous work:

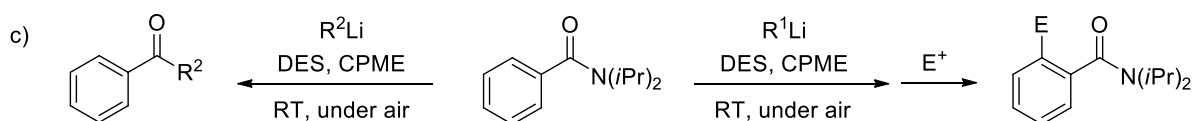
Hevia, Garcia-Alvarez, Capriati (2014-2016)^{12a,d}



Hevia, Garcia-Alvarez, Capriati (2017-2018)^{12b-c,f}



This work:

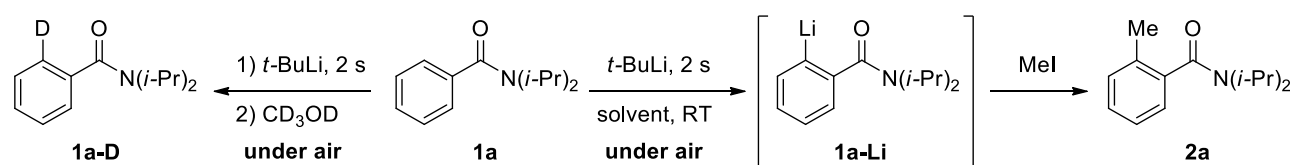


Scheme 1. (a) Addition reactions of organometallics to carbonyl compounds in DESs or water; (b) Addition reactions of organometallics to imines and nitriles in DESs or water; (c) *ortho*-Lithiation and nucleophilic acyl substitution of a benzamide derivative in ethereal/eutectic mixtures.

Building on our long-standing interest in polar organometallic chemistry^[14] and recent findings in using water or DESs as privileged reaction media with organometallics,^[12d-f, 13, 15] we now report a systematic study on the usefulness of DESs as sustainable media for promoting chemoselective *DoM* or *S_NAc* processes starting from the same carboxylic acid amide. Notable features of our report include: (a) divergent synthetic pathways according to the nature of the lithiating reagent, (b) direct *ortho*-functionalization of benzamides and ketones synthesis in DES, (c) ability to telescope *ortho*-metalation/Suzuki-Miyaura transformations in a one-pot process to synthesize valuable “building blocks”, d) absence of VOCs.

We began our investigation using *N,N*-diisopropylbenzamide **1a** as a model substrate since it is known to be completely resistant nucleophilic attack by alkyllithiums at the amide carbonyl, and to be easily *ortho*-functionalized in a total chemoselective fashion with *t*-BuLi, *sec*-BuLi or even *n*-BuLi as the lithiating agents.^[3a, 3b, 16] In a preliminary experiment, amide **1a** (0.2 mmol) was suspended in a prototypical choline chloride (ChCl)/glycerol (Gly) eutectic mixture (1:2 mol/mol) and then reacted at RT in air with a commercial 1.7 M pentane solution of *t*-BuLi (2 equiv) under continuous stirring. Quenching the reaction mixture with MeI (5 equiv) after 2 s, however, led to quantitative recovery of **1a** after work up (Table 1, entry 1). When *t*-BuLi (2 equiv) was added in one portion to a suspension of **1a** (0.2 mmol) (previously solubilized in a small amount of CPME (0.2 mL), 1 M)^[17] in the above eutectic mixture, under air at RT and with vigorous stirring to generate an emulsion, and then quenched after 2 s with MeI (5 equiv), the *ortho*-methylated adduct **2a** was this time isolated in 70% yield as the sole product (Table 1, entry 2). No traces of any nucleophilic addition product were detected by ¹H NMR and GC-MS analyses of the crude reaction mixture when amide **1a** was treated with *t*-BuLi either in the presence or in the absence of electrophile. Under these conditions, ²H NMR analysis of the deuterated product **1a-D**, resulting from the treatment of **1a** with *t*-BuLi followed by quench with CD₃OD, disclosed a selective incorporation of deuterium at the *ortho* position in up to 86% (83% yield) (see Supporting Information) (Table 1, entry 3).

Table 1. Metalation reaction of *N,N*-diisopropylbenzamide **1a** using *t*-BuLi under different conditions.^[a]



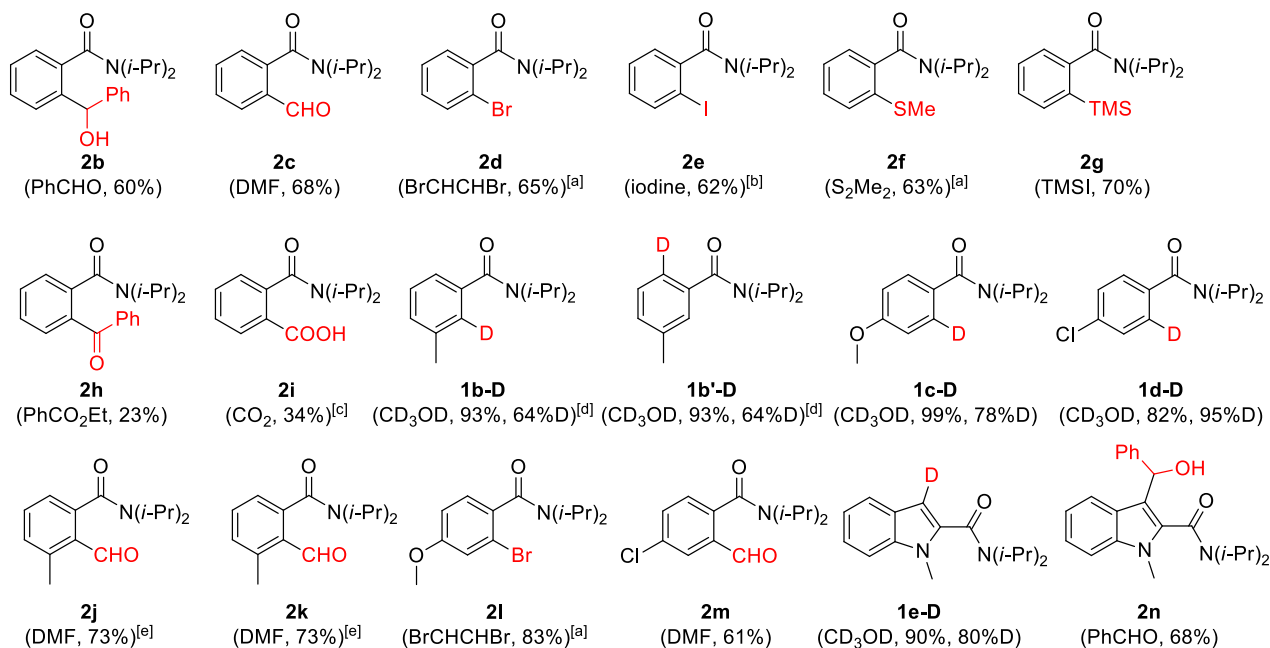
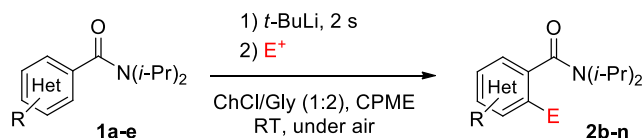
Entry	Solvent	<i>t</i> -BuLi (eq.)	E ⁺ (eq.)	Product (yield %) ^[b]
1	ChCl/Gly	2	MeI (5)	-
2	ChCl/Gly ^[c]	2	MeI (5)	2a (70)
3	ChCl/Gly ^[c]	2	CD ₃ OD (5)	1a-D (83) ^[d]
4	ChCl/Gly ^[c,e]	2	MeI (5)	2a (67)
5	ChCl/Gly ^[c]	1.5	MeI (5)	2a (60)
6	ChCl/Gly ^[c]	2	MeI (3)	2a (46)
7	ChCl/urea ^[c]	2	MeI (5)	2a (67)
8	ChCl/H ₂ O ^[c]	2	MeI (5)	-
9	H ₂ O	2	MeI (5)	-
10	Gly	2	MeI (5)	-
11	CPME	2	MeI (5)	2a (41)

[a] Reaction conditions: 1.0 g DES per 0.2 mmol of **1a**; DES: ChCl/Gly (1:2 mol mol⁻¹); ChCl/urea (1:2 mol mol⁻¹); ChCl/H₂O (1:2 mol mol⁻¹). [b] Determined by ¹H NMR using CH₃NO₂ as the internal standard. [c] CPME: 0.2 mL. [d] 86% D incorporation. [e] T = 0 °C.

No significant changes were observed when the reaction was run at 0 °C (Table 1, entry 4). Efforts were made to further improve the conversion of the starting material. Lowering the organolithium from 2 to 1.5 equiv and the electrophile from 5 to 3 equiv led to a decrease of conversion (Table 1, entries 5,6). Next, we evaluated the half-life of **1a-Li** in the above protic medium. Experiments were designed to show the reaction progress over time with reaction samples quenched with MeI at different times following treatment of the substrate **1a** with *t*-BuLi. The first-order plot obtained indicated an estimated half-life for **1a-Li** of 6.26 s (see Supporting Information). Switching ChCl/urea (1:2 mol/mol) for ChCl/Gly led to similar results (Table 1, entry 7), whereas the use of water as HBD as well as the replacement of the eutectic mixture with water or glycerol was ineffective (Table 1, entries 8-10). When using pure CPME as the solvent, *ortho*-functionalized product **2a** was obtained, albeit in 41% yield (Table 1, entry 11).

The scope and limitation of this transformation was then evaluated for a series of electrophiles and different benzamide derivatives. Electrophiles such as benzaldehyde, DMF and various halogenating, sulfonylating and silylating agents reacted smoothly with anion **1a-Li**, thereby providing the expected *ortho*-functionalized adducts **2b-2g** in good yields (60–70%) (Scheme 2). The quenching reaction of **1a-Li** with base-sensitive functional groups (e.g. esters) and CO₂ was less favourable and furnished the aromatic ketone **2h** and the carboxylic acid derivative **2i** in 23–34% yield (Scheme 2). Amide derivatives bearing electron-withdrawing or electron-donating groups on the aromatic ring were also tested. Metalation-deuteration of **1b-d** always took place proximal to the amide moiety (up to 95%D), (a) both at the *ortho* and at the *ortho'* position in the case of **1b** (and not in competition with lateral lithiation) and (b) leaving the chloride unreacted in the case of **1d**, and thus available for further functionalisation (Scheme 2). Formylation of *ortho*-lithiated **1b** with DMF afforded products **2j,k** in 73% yield, however as an inseparable 1:1 mixture of regioisomers. On the other hand, bromination and formylation of *ortho*-lithiated **1c-Li** and **1d-Li** regioselectively led to products **2l,m** in 61–83% yield. Interestingly, indole derivative **1e** showed 90% deuterium incorporation at the 3-position when sequentially treated with *t*-BuLi and CD₃OD (see ²H NMR analysis, Supporting Information), and provided product **2n** in 68% yield when anion **1e-Li** was quenched with PhCHO.

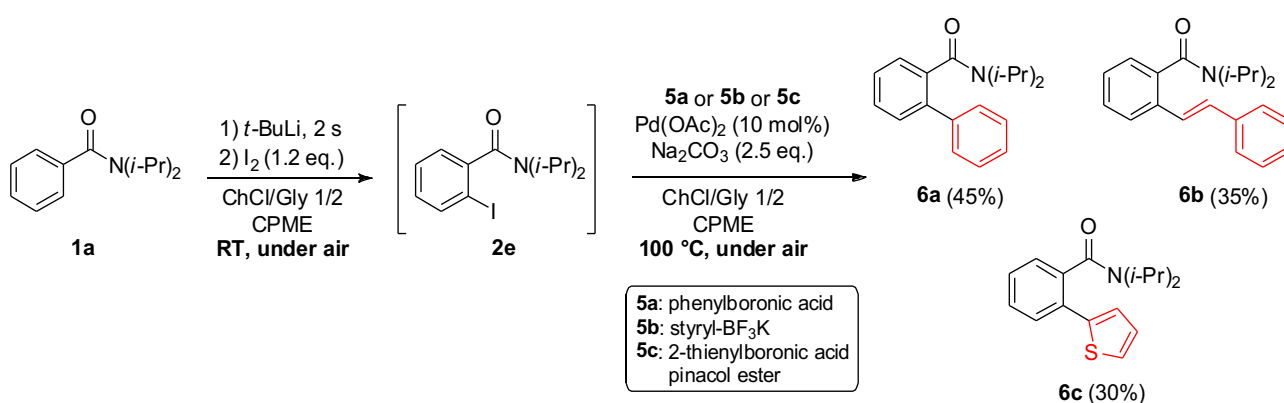
1a: *N,N*-diisopropylbenzamide
1b: *N,N*-diisopropyl-3-methylbenzamide
1c: *N,N*-diisopropyl-4-methoxybenzamide
1d: 4-chloro-*N,N*-diisopropylbenzamide
1e: *N,N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide



Scheme 2. Scope of the *ortho*-lithiation reaction of *N,N*-diisopropylbenzamides **1a-e** in CPME/DES (ChCl/Gly 1:2 mol mol⁻¹) mixture. Reaction conditions: **1a-e** (0.2 mmol), *t*-BuLi (1.7 M in pentane, 0.4 mmol), CPME (0.2 mL), DES (1.0 g), electrophile (5 equiv unless otherwise stated). The yields reported are for products isolated after flash column chromatography. [a] The amount of the electrophile can be reduced to 1.2 equiv without any loss in terms of yield. [b] I₂ was added as a 2 M solution in 2-MeTHF. [c] CO₂ was bubbled for 15 s. [d] Overall percentage yield and overall percentage deuteration (ratio **1b-D**:**1b'-D** = 1:1). [e] Overall percentage yield (ratio **2j**:**2k** = 1:1).

We then explored the reactivity of our model substrate **1a** toward other organolithium reagents. When amide **1a** was treated in a CPME/DES (ChCl/Gly 1:2) mixture at RT under air with *sec*-BuLi either in the presence or in the absence of MeI as the electrophile, only the starting material was recovered. Alternatively, using *n*-BuLi (2 equiv) as the nucleophilic reagent, only a mixture of valerophenone **3a** and alcohol **4a** in a 5:1 molar ratio (85% conversion) was detected in the crude reaction mixture after 20 s (Table 2, entry 1). When amide **1a** was treated with *n*-BuLi (2 equiv) in a CPME/DES (ChCl/Gly 1:2) mixture and quenched after 2 s using MeI as the electrophile, ketone **3a** and alcohol **4a** were formed in the same 5:1 ratio as the sole products. Such a remarkable chemoselectivity toward the S_NAc pathway was similarly observed upon replacing the Gly

The design of telescoped, one-pot processes involving multiple stoichiometric/catalytic events, such as those set up by assembling main group-mediated organic transformations and transition-metal-catalysed reactions, are attractive methodologies in the toolbox of synthetic chemistry for their intrinsic practical and economical advantages (e.g., minimisation of chemical waste, significant save of time and energy, and circumvention of purification phases).^[19] We recently found out that the environmentally responsible eutectic mixture ChCl/Gly (1:2) was an effective reaction medium for performing ligand-free, chemoselective Suzuki-Miyaura (SM) couplings that proceeded in air and under generally mild conditions.^[18] Thus, we targeted telescoped DoM-SM approaches for the preparation of more functionalized amides based on a preliminary, regioselective *ortho*-lithiation/iodination of amide **1a** followed by an *in situ* Pd-catalysed SM reaction in the above-described eutectic mixture using different borates/boronic acids as nucleophilic partners. To this end, amide **1a** was first treated with *t*-BuLi in the ChCl/Gly/CPME mixture and then quenched after 2 s with a stoichiometric amount of iodine (1.2 equiv).^[19] The resulting *ortho*-iodo derivative **2e** was finally subjected to a SM coupling reaction with phenylboronic acid (**5a**) or styryl potassium trifluoroborate (**5b**) or 2-thienylboronic acid pinacol ester (**5c**), by using 10 mol% of Pd(OAc)₂ as the catalyst and in the absence of any additional ligand, thereby affording valuable *ortho*-functionalized styryl or (hetero)aryl derivatives **6a-c** in yields of up to 45% after two steps in one pot (Scheme 3).



Scheme 3. Telescoped DoM/Suzuki–Miyaura arylation/vinylation of amide **1a** in a ChCl/Gly/CPME mixture.

In summary, directed *ortho* metalation or nucleophilic acyl substitution processes, en route to functionalized amides and ketones, can be conveniently and regioselectively carried out starting from the same aromatic carboxylic acid amide using environmentally friendly eutectic mixtures (working under air, at RT or 0 °C)

depending on the nature of the organolithium reagent. The use of *t*-BuLi led to *ortho*-lithiation processes, while the use of less sterically encumbered organolithium reagents led to S_NAc reactions. The low levels of tertiary alcohol by-products suggests that the DES plays a prominent role in stabilizing the tetrahedral intermediates. In addition, we have demonstrated the possibility of performing one-pot, telescoped *ortho*-lithiation/Pd-catalysed Suzuki–Miyaura coupling reactions in DES mixtures, which are of great value in terms of efficiency and environmental sustainability. Further extensions of this work are currently underway in our laboratories and results will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: deep eutectic solvents; directed *ortho*-metalation; nucleophilic addition; organolithium reagents; green chemistry.

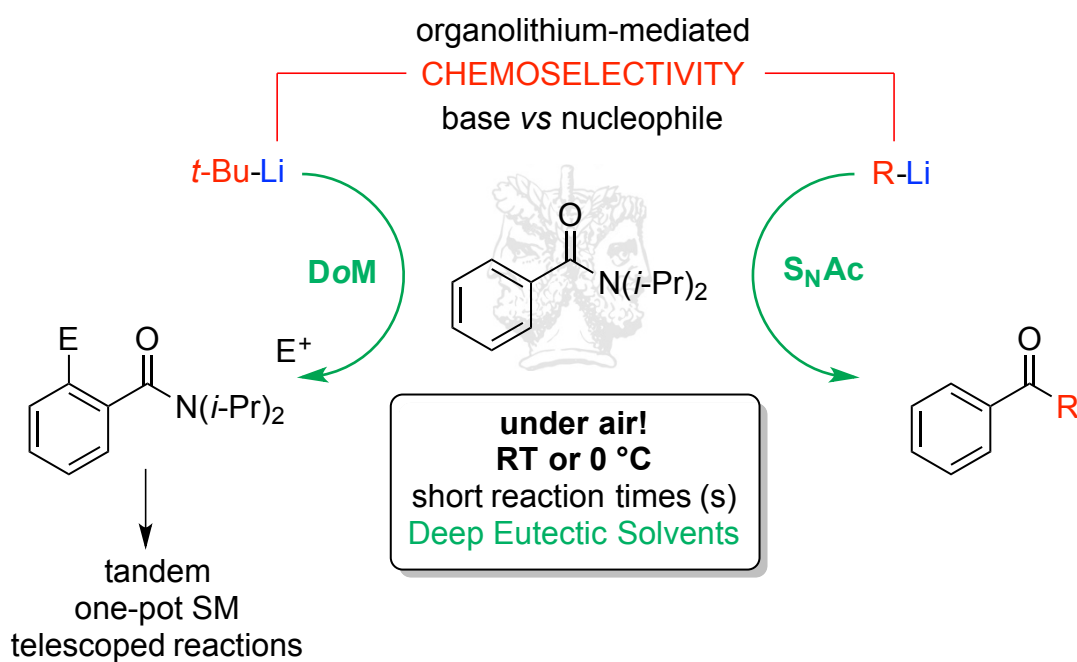
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- [19] The use of less than 5 eq. of iodine was mandatory in order to avoid the undesired iodination of boron derivative.

Graphical abstract



Janus-faced reactivity of carboxylic acid amides in Deep Eutectic Solvents (DESs) with organolithium reagents! Highly chemoselective and fast directed *ortho* metalation (DoM) or nucleophilic acyl substitution ($\text{S}_{\text{N}}\text{Ac}$) processes proceed smoothly in DESs, at room temperature or 0 °C and under air, depending on the nature of the organolithium reagent.

