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Chemo- and regioselective anionic Fries rearrangement promoted by lithium amides under aerobic conditions in sustainable reaction media

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Dedicated to the memory of Professor Victor Snieckus

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Supporting Information for this article is given via a link at the end of the document.

Abstract: A straightforward and efficient protocol to promote the metalation/anionic Fries rearrangements of *O*-aryl carbamates, using for the first time a lithium amide as metalating agent under aerobic/ambient-friendly reaction conditions, is reported. This approach enables the sustainable preparation of salicylamide derivatives with high levels of chemoselectivity within ultrafast reaction times, working at room temperature in the presence of air/moisture, and using the environmentally responsive cyclopentyl methyl ether as a solvent. Furthermore, the regioselective manipulation of *O*-2-tolyl carbamates has been accomplished using interchangeably alkyllithiums or lithium amides, with an unexpected beneficial contribution from the employment of biorenewable protic eutectic mixtures as non-innocent reaction media.

Introduction

The directed *ortho*-metalation (D*o*M) of *O*-aryl carbamates[1] represents nowadays a general and powerful strategy for the assembly of regiospecifically substituted (hetero)aromatic derivatives with a wide range of applications.[2] Aromatic carbamates are cleanly *ortho*-metalated by alkyllithiums,[3] lithium or sodium amides,[4] and heterometallic bases[5] at low temperatures, allowing synthetically useful functionalizations upon electrophilic quench. Furthermore, in the absence of an external electrophile the *o*-aryl anion undergoes an intramolecular carbamoyl transfer upon slow warming to room temperature, leading to functionalized salicylamides which can be subjected to further D*o*M chemistry manipulations (Figure 1, A).[6] This process, known as the anionic *ortho*-Fries rearrangement (A*o*F),[7] has been developed by Snieckus in 1983[8] and thoroughly investigated by several research groups both under its mechanistic and synthetic aspects.[9] However, strictly controlled experimental conditions (low temperature, dry ethereal solvents, and inert atmosphere) are typically required to avoid undesired degradation pathways or side reactions.[10] The development of new sustainable protocols which enable the use of aerobic/protic conditions in alkali-metal-mediated transformations has profoundly reshaped the conceptual chemistry of these highly polar organometallic reagents.[11] In this context, we recently reported that alkyllithiums can efficiently promote either chemo- and regioselective D*o*M,[12] benzylic metalation[13] and nucleophilic acyl substitution (S_NAc)[14] reactions using both deep eutectic solvents (DESs) and cyclopentyl methyl ether (CPME)[15] as sustainable reaction media, working at room temperature, under

air/moisture. Notwithstanding the use of lithium amides is a well consolidated methodology to promote D*o*M reactions using classical Schlenk techniques,[16] their reactivity as metalating agents under aerobic conditions remains however unexplored. To date, only few examples on their nucleophilic behaviour in hydroamination[17] and (trans)amidation[18] reactions have been recently reported in 2-MeTHF in the presence of air and moisture. On these bases, we now report a systematic study on the usefulness of hindered lithium amides to promote the metalation/Fries rearrangement of *O*-aryl carbamates, using both CPME and DESs as sustainable reaction media under bench-type aerobic conditions (Figure 1, B).

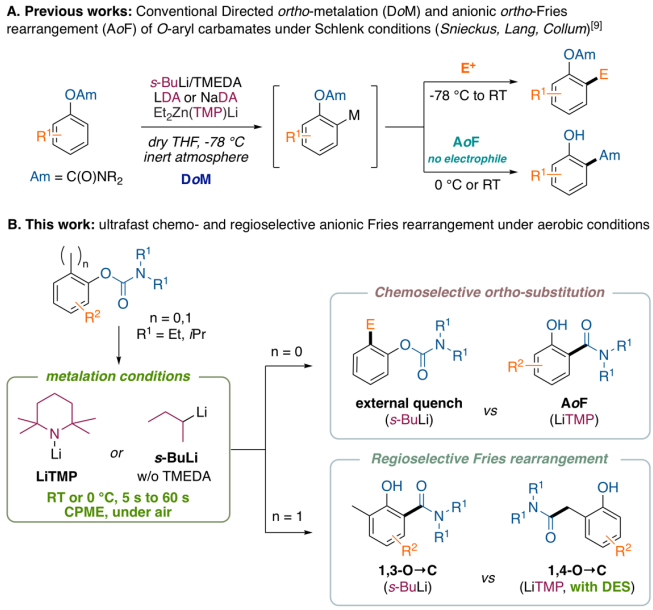


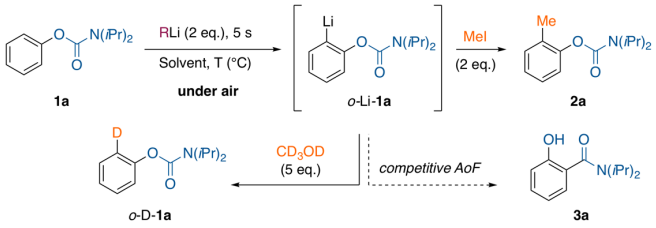
Figure 1. (A) State-of-the-art of the A*o*F rearrangement and (B) aim of the work.

Notable features of our report include: a) the unprecedented use of lithium amides as metalating agents to promote ultrafast D*o*M/A*o*F processes with excellent selectivities and broad functional groups tolerance under aerobic conditions, b) the beneficial and crucial role of eutectic mixtures on the chemo- and regioselectivity of the 1,4- (*homo*-Fries) migration and (c) of high synthetic value, the possibility to perform a fast electrophilic trapping of the kinetic metalation product under thermodynamic conditions.

Results and Discussion

The *ortho*-lithiation step of the D*o*M/AoF sequence under bench-type aerobic conditions has been firstly investigated using the *O*-phenyl *N,N*-diisopropylcarbamate **1a** as a model substrate, since (a) bulky *N*-substituents prevent the competitive nucleophilic addition at the amide carbonyl and (b) the corresponding *o*-Li-**1a** species does not undergo competitive A*o*F rearrangement at low temperatures.[1] Based on our previous findings, a vigorously stirred suspension[19] of **1a** (0.2 mmol, 0.7 M in CPME) in a prototypical ChCl/Gly (1:2 mol mol^{-1}) eutectic mixture was reacted with *t*-BuLi (1.7 M in pentane, 2 eq.) at RT under air. Rapid quench (5 s) of the reaction mixture with MeI (2 eq.) afforded the corresponding *ortho*-methylated analogue **2a** in 35% yield (Table 1, entry 1), alongside with 44% of salicylamide **3a** resulting from the competitive intramolecular carbamoyl transfer process (A*o*F).

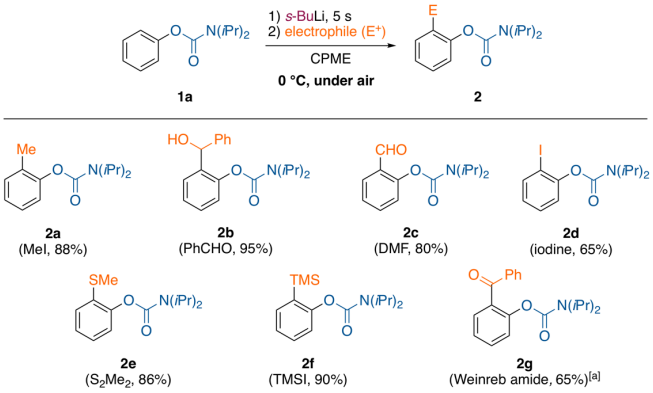
Table 1. Metalation of *O*-phenyl *N,N*-diisopropylcarbamate **1a** under different conditions.



Entry	RLi	T (°C)	Product	% yield[a]	
				CPME/DES	CPME
1	*t*-BuLi	25	**2a**	35[b]	29[b]
2	*t*-BuLi	0	**2a**	80	86
3	*n*-BuLi	0	**2a**	59	81
4	*s*-BuLi	0	**2a**	61	90 (92)[c]
5	LiTMP	0	**2a**	68[d]	80[d]
6	*s*-BuLi	0	*o*-D-**1a**	45[e]	92[f]

Reaction conditions: **1a** (0.2 mmol), RLi (0.4 mmol) under vigorous stirring, electrophile (2 eq.). Solvent: CPME (0.3 mL), ChCl/Gly 1:2 mol mol^{-1} (1 g) *or* CPME (1 mL). [a] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [b] **3a**: 44% (CPME/DES), 59% (CPME). [c] Under N_2 in dry CPME. [d] Yield reported as sum of **2a** and *O*-2-ethylphenyl-*N,N*-diisopropylcarbamate. [e] Isolated yield, 54% D incorporation. [f] Isolated yield, 99% D incorporation.

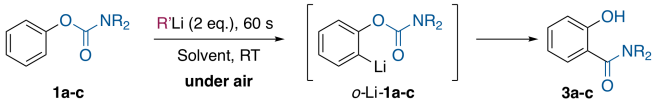
Similar results were obtained using CPME (1 mL, 0.2 M) as the sole reaction medium (entry 1), while running the reaction at 0 °C significantly improved the yield of **2a** both under heterogeneous and homogeneous conditions (entry 2), without the formation of any A*o*F or S_NAc byproducts. Less reactive but easy-to-handle alkyllithiums efficiently promoted the D*o*M of **1a** (entries 3-4), and the highest yield of **2a** (90%) was obtained using *s*-BuLi in CPME at 0 °C without the need of common activators such as TMEDA (entry 4). Under classical Schlenk conditions (inert atmosphere, dry CPME) comparable results were obtained (entry 4). This testifies that the use of aerobic conditions for this transformation is both feasible and fruitful. Pleasingly, treatment of **1a** with a freshly prepared 1 M solution of LiTMP in 2-MeTHF[20] at 0 °C under air led to an efficient *o*-lithiation using both CPME/DES (**2a**, 68%) and CPME (**2a**, 80%) as reaction media (entry 5), disclosing the hitherto unexplored effectiveness of lithium amides as metalating agents under aerobic conditions. ^{2}H NMR analysis of the product *o*-D-**1a**, arising from the treatment of **1a** with *s*-BuLi in CPME at 0 °C followed by quench with CD_3OD, showed highly selective *o*-metalation with 99% D incorporation, however with lower efficiency under heterogeneous conditions (54% D) confirming the general decrease of the metalation performance in the presence of protic eutectic mixtures (entry 6). Other electrophiles, such as aldehydes, sulfurylating (S_2Me_2), silylating (TMSI), halogenating (iodine) and acylating agents reacted smoothly with *o*-Li-**1a** using CPME as the sole reaction medium, thereby providing the expected *ortho*-functionalized adducts **2b-g** in good to excellent yields (65-95%, Scheme 1).



Scheme 1. Electrophilic functionalization of **1a** under aerobic conditions. Reaction conditions: **1a** (0.2 mmol), *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol), CPME (1 mL), electrophile (2 eq.). Reported yields refer to isolated products. [a] Weinreb amide: *N*-methoxy-*N*-methylbenzamide.

Further efforts have been then devoted to privilege the A*o*F rearrangement pathway of *O*-aryl carbamates under aerobic conditions. Within only 60 s salicylamide **3a** was recovered in a quantitative yield (98%) when a solution of **1a** (0.2 M in CPME) was reacted with *s*-BuLi (2 eq.), at room temperature under air, in the absence of an external electrophile (Table 2, entry 1). Metalation of **1a** with other alkyllithiums was less effective (entries 2-3) resulting in a loss of selectivity due to the formation of undesired S_NAc (*n*-BuLi) or dearomatization byproducts (*t*-BuLi)[21] in non-negligible amounts. Remarkably, metalation of **1a** with LiTMP delightfully led to the quantitative recovery of **3a** (98%, entry 5), and even the less basic LDA promoted the formation of the Fries product **3a** albeit in a moderate 34% yield (entry 4). As expected, the use of ChCl/Gly (1:2 mol mol^{-1}) in combination with CPME as reaction media prevented the total conversion of **1a** due to the competitive protonolysis (entry 6), and no improvements were observed using other organolithiums or replacing Gly with

Table 2. D*o*M/Fries-rearrangement of carbamates **1a-c** under different conditions.



R = *i*Pr (**1a**), Et (**1b**), Me (**1c**)

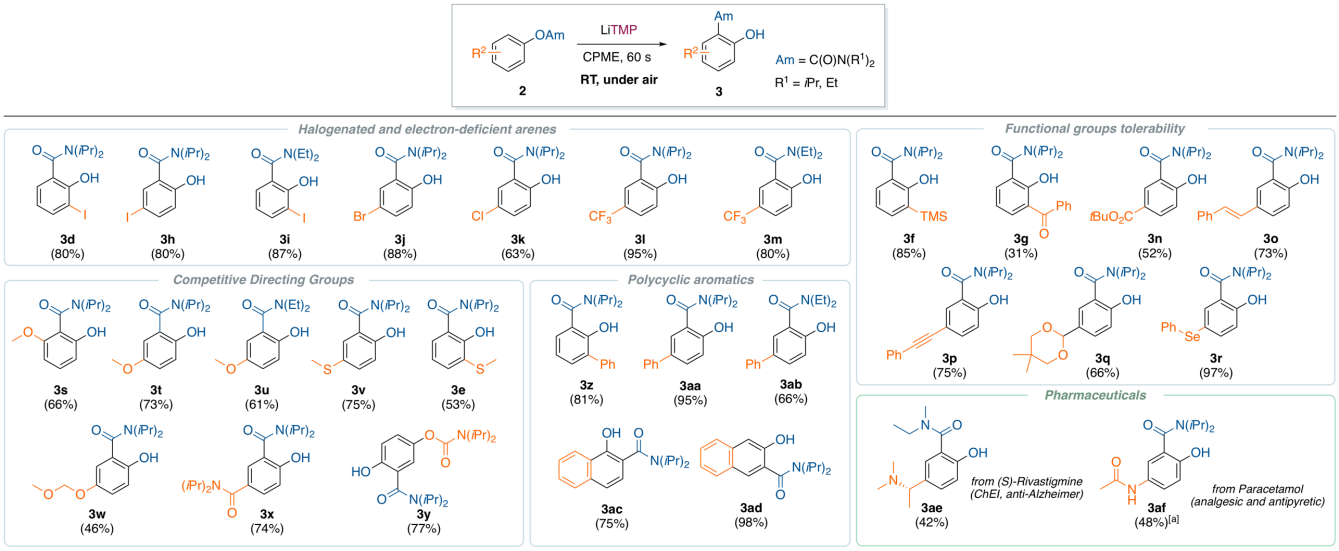
Entry	Substrate	Solvent	R'Li (2 eq.)	**3** (%)[a]
1	**1a**	CPME	*s*-BuLi	**3a** (98)
2	**1a**	CPME	*n*-BuLi	**3a** (77)
3	**1a**	CPME	*t*-BuLi	**3a** (61)
4	**1a**	CPME	LDA	**3a** (34)
5	**1a**	CPME	LiTMP	**3a** (98)
6	**1a**	ChCl/Gly 1:2[b]	*s*-BuLi	**3a** (62)
7	**1b**	CPME	*n*-BuLi	-[c]

8	**1b**	CPME	*s*-BuLi	-[c]
9	**1b**	CPME	*t*-BuLi	**3b** (56)
10	**1b**	CPME	LiTMP	**3b** (85)
11	**1c**	CPME	LiTMP	-[c]

Reaction conditions: **1a-c** (0.2 mmol), RLi (0.4 mmol), CPME (1 mL), 60 s, under air. [a] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [b] 1 g of ChCl/Gly (1:2 mol mol^{-1}) and 0.3 mL of CPME per 0.2 mmol of **1a**. [c] Only S_NAc products were detected.

other HBDs (Table S2). Unsurprisingly, the less hindered *N,N*-diethylcarbamate **1b** afforded only S_NAc products when reacted both with *n*-BuLi and *s*-BuLi, whereas only *t*-BuLi was able to promote the formation of **3b** in a moderate 56% yield (entries 7-9). Noteworthy, metalation of **1b** using LiTMP proceeded in a totally chemoselective fashion, and the A*o*F product **3b** was recovered in excellent yield (85%) after workup (entry 10).[22] This remarkable result disclosed that the use of easy-to-handle LiTMP as metalating agent under aerobic conditions is crucial for this kind of transformation since potentially allows (a) the use of easily hydrolysable aryl carbamates and (b) chemoselective metalation reactions in the presence of other organolithiums-sensitive functionalities on the aromatic ring.

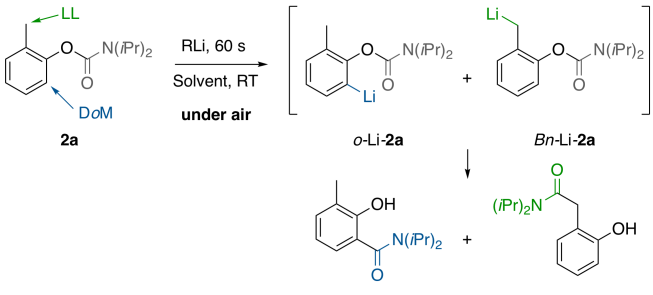
With satisfactory conditions in place, the scope and limitations of this transformation were evaluated for a series of functionalized *O*-aryl *N,N*-dialkylcarbamates **2** (Scheme 2), using the commodity metalating agent LiTMP in CPME under air. Pleasingly, the reaction proceeded smoothly en route to iodinated (**3d, 3h-i**) and brominated (**3j**) derivatives (80-88%) without competitive X-Li exchange.[23] Chlorinated (**3k**) and trifluoromethylated (**3l-m**) salicylamides were also recovered in good overall yields (63-95%) upon treatment of their parent highly reactive carbamates. Remarkably, our methodology allowed the chemoselective preparation of salicylamides **3f-g** and **3n-r**, bearing several organolithium-sensitive functional groups, without competitive pathways such as remote □-silyl lithiation (**3f**),[24] nucleophilic addition (**3g**, **3n**), carbolithiation (**3o-p**), α-lithiation (**3q**) or transmetalation (**3r**) reactions. A series of competition metalation experiments disclosed that the *O*-aryl carbamate DMG preserve its powerful directing ability under thermodynamic aerobic conditions. Electron-rich arenes bearing weak DMGs such as methoxy (**2s-u**) or thioether (**2e**, **2v**) were regioselectively metalated by LiTMP proximal to the carbamate moiety (a) exclusively at the 2-position for **2s**[25] and (b) without competitive α-lithiation to sulphur (**2e**, **2v**),[26] affording amides **3e**, **3s-v** in good yields (53-73%). Excellent regioselectivities were observed even in the presence of strong DMGs such as methoxymethyl (MOM) ether (**3w,** 46%), tertiary amide (**3x**, 74%), and another carbamate which provided the sole single carbamoyl transfer product **3y** (77%). The D*o*M/A*o*F migration reaction proceeded with satisfactory results for a series of polyaromatic carbamates, releasing the biphenyl derivatives **3z**, **3aa-ab** (66-95%) and 1-hydroxy-2-naphthamide **3ac** in 75% yield without any remote or *peri*-metalation byproducts.[27]



Scheme 2. LiTMP-promoted A*o*F rearrangement of *O*-aryl carbamates **2** in CPME under aerobic conditions. Reaction conditions: **2** (0.2 mmol), LiTMP (1 M in 2-MeTHF, 0.4 mmol), CPME (1 mL), 60 s, RT, under air. Reported yields refer to isolated products. [a] Reaction conditions: **2af** (0.2 mmol), *s*-BuLi (1.4 M in cyclohexane, 0.6 mmol), 2-MeTHF (1 mL), 60 s, under air.

Remarkably, under these conditions the *O*-2-naphthyl carbamate **2ad** was metalated by LiTMP with an unprecedented regioselectivity at the 2-position leading to the exclusive formation of salicylamide **3ad** (98%).[28] The potential of our methodology has been illustrated with the late-stage functionalization of the anti-Alzheimer drug (*S*)-Rivastigmine[29] and the corresponding carbamate of the analgesic agent paracetamol. Treatment of Rivastigmine with LiTMP gave access to the corresponding salicylamide **3ae**, however in moderate yield. On the other hand, metalation of paracetamol carbamate with LiTMP was ineffective, whereas only the use of *s*-BuLi (3 eq.) as metalating agent led to the desired amide **3af** in a satisfactory 48% yield.

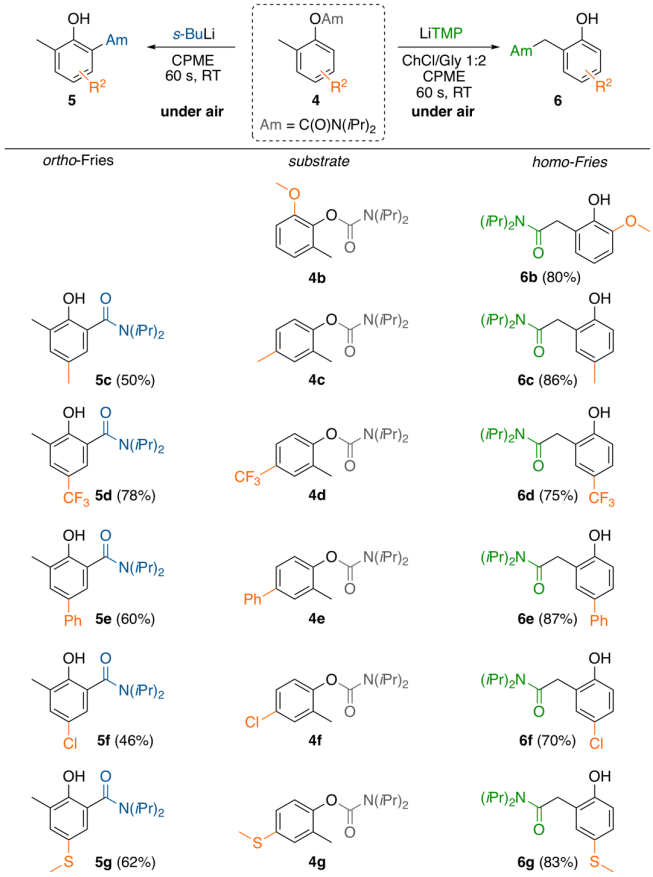
A series of experiments has been next performed on the *O*-2-tolyl *N,N*-diisopropylcarbamate **2a** to gain more insight into the regioselectivity of the metalation/migration sequence under aerobic conditions (Scheme 3), since deprotonation of **2a** can occur both at the *ortho*- and at the benzylic positions with consequent A*o*F (1,3-O-C) or *homo*-Fries (1,4-O-C)[30] rearrangements. Metalation of **2a** with *s*-BuLi in CPME, at RT and under air, afforded the sole *ortho*-Fries product **5a** in a remarkable 88% yield. Although the reaction outcome is presumably driven by the relative stabilities of the corresponding phenoxide leaving groups,[9b] treatment of **2a** with *s*-BuLi in the presence of a heterogeneous mixture of CPME/DES led to an unexpected 1:1 mixture of *ortho*- (**5a**) and *homo*-Fries (**6a**) products (Scheme 3, entry 2), suggesting a putative stabilizing effect of the eutectic mixture upon the *homo*-Fries phenolate anion. Lithiation of **2a** with LiTMP proceeded with high efficiency and in a total regioselective fashion only under heterogeneous conditions (Scheme 3, entry 3), whereas only an unresolved complex mixture of products was recovered in the absence of DES. These results disclose the beneficial active role of the protic deep eutectic mixture in the lateral lithiation/*homo*-Fries rearrangement reaction, since the commonly detrimental competitive protonolysis of the organolithium might prevent a further benzylic metalation of the rearranged product **6a** and the formation of intermolecular addition byproducts.[9b]



entry	RLi (2 eq.)	Solvent	*ortho-Fries (1,3-O-C)* (yield %)[a]		*homo-Fries (1,4-O-C)* (yield %)[a]
1	*s*-BuLi	CPME	88	:	0
2	*s*-BuLi	ChCl/Gly 1:2 / CPME	51	:	44
3	LiTMP	ChCl/Gly 1:2 / CPME	0	:	80
4	LiTMP	CPME	0	:	10

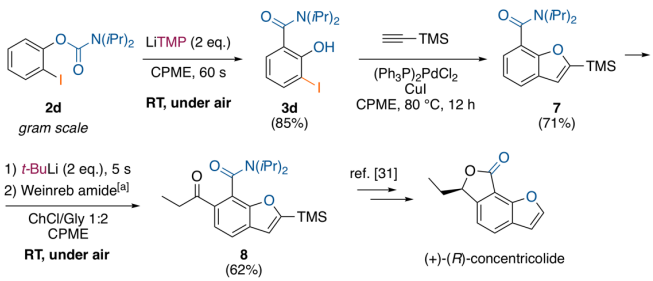
Scheme 3. Regioselective anionic Fries rearrangement of **2a**. Reaction conditions: **2a** (0.2 mmol), RLi (0.4 mmol), ChCl/Gly 1:2 mol mol^{-1} (1 g)/CPME (0.3 mL) *or* CPME (1 mL). [a] Isolated yields.

A series of *ortho*-tolyl carbamates **4** decorated with different strong (**4b**, **4g**) and weak (**4c**) EDG, EWG (**4d**), aryl (**4e**) and halogenated (**4f**) substituents on the aromatic ring were subjected to optimized metalation conditions to generate the corresponding 1,2,3-contigously substituted salicylamides **5c-g** (46-78%) and the homologous α-arylacetamide derivatives **6b-g** (70-86%) with outstanding regioselectivities (Scheme 4).



Scheme 4. Regioselective *ortho- vs homo*-Fries rearrangement of **4b-g**. Reaction conditions: **4b-g** (0.2 mmol), RLi (0.4 mmol), solvent, 60 s, under air. Solvent: CPME (1 mL) *or* ChCl/Gly 1:2 mol mol^{-1} (1 g)/CPME (0.3 mL). The yields reported refers to isolated products.

To further highlight the utility and the robustness of our methodology, we finally envisaged a sustainable reinterpretation of the synthetic sequence for the preparation of benzofuran carboxamide **8**,[31] a key building block in the total synthesis of the anti-HIV-1 agent (+)-(*R*)-concentricolide[32] (Scheme 5).



Scheme 5. Synthesis of benzamide **8** under sustainable reaction conditions starting from **2d**. Yields reported refer to isolated products. [a] Weinreb amide: *N*-methoxy-*N*-methylpropionamide.

Remarkably, the LiTMP-promoted A*o*F of *O*-2-iodophenyl carbamate **2d** in CPME has been easily scaled-up to 4 mmol (1.4 g) with comparable efficiencies both in terms of yield and chemoselectivity. A simple acid-base workup procedure allowed the recovery both of pure **3d** (85%) and TMP (78%, see Supporting Information for details), which can be recycled for further preparations of LiTMP. Tandem Sonogashira coupling annulation of **3d** with TMS-acetylene in CPME allowed the facile preparation of **7** (71%). Finally, *ortho*-lithiation of **7** with *t*-BuLi followed by acylation with *N*-methoxy-*N*-methylpropionamide in a CPME/DES mixture at RT under air[12] afforded the benzofuran carboxamide **8** in a satisfactory 62% yield.

Conclusion

In summary, our report discloses that the reactivity of *O*-aryl carbamates towards organolithium reagents in the presence of air and moisture, using environmentally responsible reaction media, can be conveniently controlled by changing the nature of the metalating agent. A fast and efficient protocol to access a wide variety of salicylamide derivatives, arising from the 1,3-O-C anionic Fries rearrangement of the corresponding *ortho*-lithiated *O*-aryl carbamates, has been successfully developed using for the first time a lithium amide as metalating agent in the eco-friendly solvent CPME, at room temperature and under aerobic conditions, with an unprecedented level of chemoselectivity and functional groups tolerance. Remarkably, the regioselective manipulation of *O*-2-tolyl carbamates has been successfully accomplished using interchangeably alkyllithiums or lithium amides, with an unexpected help from the employment of environmentally friendly eutectic mixtures in combination with CPME. Besides, at 0 °C our methodology also allows the facile *ortho*-functionalization of *O*-aryl carbamates resorting to an ultrafast electrophilic trapping of the kinetic metalation product, using *s*-BuLi as metalating agent without the need of toxic additives. The utility and the versatility of this new synthetic protocol have been further highlighted by its scalability and the easy recyclability/reusability of the free amine TMP, which are of great value in terms of efficiency and environmental sustainability.

Experimental section

Full experimental details and copies of NMR spectra are included in the Supporting Information.

SAFETY NOTE: Organolithiums were handled under an inert atmosphere (Schlenk techniques) until the point at which they were mixed with a solution of the substrate in CPME, under an air atmosphere and with vigorous magnetic stirring, whereupon they react quickly. No particular problems were experienced during the addition. Organolithiums, however, are notoriously prone to ignition in air, and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

Preparation of lithium 2,2,6,6-tetramethylpiperidine (LiTMP) solution in 2-MeTHF. In a Schlenk tube under a positive nitrogen pressure, *n*-BuLi (2.5 M in hexanes, 4.0 mmol, 1.0 eq.) was added to a precooled (0 °C) stirred solution of 2,2,6,6-tetramethylpiperidine (TMP) (4.4 mmol, 1.1 eq., 0.75 mL) in dry 2-MeTHF (1.51 mL). The mixture was stirred at 0 °C for 10 minutes to yield a clear yellowish solution of LiTMP that was used without further purifications.[20]

Directed *ortho*-metalation of carbamate 1a: synthesis of compounds 2a-g. Reactions were performed under air at 0 °C. In an open screw cap vial, *O*-phenyl *N,N*-diisopropylcarbamate **1a** (0.2 mmol, 1 eq., 35 mg) was dissolved in CPME (1 mL, 0.2 M), and the mixture was vigorously stirred for 5 min at 0 °C. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 5 s, then quenched with the selected electrophile (0.4 mmol, 2 eq.). The mixture was diluted with water then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

General procedure for the *ortho*-Fries rearrangement of carbamates 2: synthesis of salicylamides 3d-af. Reactions were performed under air at room temperature. In an open screw cap vial, the appropriate carbamate **1a-b**, **2d-af** (0.2 mmol, 1 eq.) was dissolved in CPME (1 mL, 0.2 M) and the mixture was stirred for 5 min. LiTMP (1 M in 2-MeTHF, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 60 s and finally quenched with water or 1 M HCl. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

General procedure for the *ortho*-Fries rearrangement of carbamates 4: synthesis of compounds 5c-g. Reactions were performed under air at room temperature. In an open screw cap vial, the selected carbamates **4c-g** (0.2 mmol, 1.0 eq.) were dissolved in CPME (1 mL, 0.2 M) and the mixture was stirred for 5 min. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 1 min and finally quenched with water or 1 M HCl. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products **5c-g** were purified by flash column chromatography on silica gel.

General procedure for the *homo*-Fries rearrangement of carbamates 4: synthesis of compounds 6b-g. Reactions were performed under air at room temperature. In an open screw cap vial, the appropriate carbamate **4b-g** (0.2 mmol, 1 eq.) was dissolved in CPME (0.3 mL), then ChCl/Gly 1:2 mol mol^{-1} (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. LiTMP (1 M in 2-MeTHF, 2 eq., 0.4 mmol) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched with water or 1 M HCl after 1 min. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products **6b-g** were purified by flash column chromatography on silica gel.

Scale-up preparation of 2-hydroxy-3-iodo-*N,N*-diisopropylbenzamide (3d) and recycle of 2,2,6,6-tetramethylpiperidine (TMP). In a 100 mL round-bottom flask, 2-iodophenyl-*N,N*-diisopropylcarbamate **2d** (4 mmol, 1 eq., 1.38 g) was dissolved in CPME (20 mL, 0.2 M) and the mixture was vigorously stirred for 5 min. LiTMP (1 M in 2-MeTHF, 8 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 60 s and finally quenched with 1 M HCl (10 mL). The aqueous layer (**A**) was removed and used for the recycle of 2,2,6,6-tetramethylpiperidine (see below). The combined organic layers were washed with NaOH 1 M (3 x 10 mL). The combined basic aqueous layers (**B**) were treated with HCl 1 M until pH = 6 and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure to give **3d** as white solid (1.18 g, 85%). The acidic aqueous layer (**A**) containing 2,2,6,6-tetramethylpiperidine hydrochloride, was treated with aqueous 1 M NaOH solution until pH = 10, and then extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure to give 2,2,6,6-tetramethylpiperidine (TMP) as pale-yellow liquid (0.44 g, 78%).

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933.

[2] A. K. Ghosh, M. Brindisi, *J. Med. Chem.* **2015**, *58*, 2895-2940.

[3] M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni, V. Snieckus, *Eur. J. Org. Chem.* **2018**, *2018*, 447-454.

[4] a) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 9051-9057; b) K. J. Singh, A. C. Hoepker, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 18008-18017.

[5] a) L. Balloch, A. R. Kennedy, R. E. Mulvey, T. Rantanen, S. D. Robertson, V. Snieckus, *Organometallics* **2011**, *30*, 145-152; b) F. García, M. McPartlin, J. V. Morey, D. Nobuto, Y. Kondo, H. Naka, M. Uchiyama, A. E. H. Wheatley, *Eur. J. Org. Chem.* **2008**, *2008*, 644-647.

[6] M. P. Sibi, S. Chattopadhyay, J. W. Dankwardt, V. Snieckus, *J. Am. Chem. Soc.* **1985**, *107*, 6312-6315.

[7] M. Korb, H. Lang, *Chem. Soc. Rev.* **2019**, *48*, 2829-2882.

[8] M. P. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1935-1937.

[9] a) M. Korb, H. Lang, *Eur. J. Inorg. Chem.* **2021**, e202100946; b) M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni, V. Snieckus, *Eur. J. Org. Chem.* **2018**, *2018*, 440-446; c) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691-694; d) R. E. Miller, T. Rantanen, K. A. Ogilvie, U. Groth, V. Snieckus, *Org. Lett.* **2010**, *12*, 2198-2201; e) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem. Int. Ed.* **2008**, *47*, 2097-2101; *Angew. Chem.* **2008**, *120*, 2127-2131; f) K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753-13760; g) M. Kauch, V. Snieckus, D. Hoppe, *J. Org. Chem.* **2005**, *70*, 7149-7158; h) O. Middel, Z. Greff, N. J. Taylor, W. Verboom, D. N. Reinhoudt, V. Snieckus, *J. Org. Chem.* **2000**, *65*, 667-675; i) J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, H. Hu, *J. Org. Chem.* **1994**, *59*, 5147-5148.

[10] U. Wietelmann, J. Klett, *Z. Anorg. Allg. Chem.* **2018**, *644*, 194-204.

[11] a) F. M. Perna, P. Vitale, V. Capriati, *Curr. Opin. Green Sustain. Chem.* **2021**, *30*, 100487; b) S. E. Garcia-Garrido, A. Presa Soto, E. Hevia, J. Garcia-Alvarez, *Eur. J. Inorg. Chem.* **2021**, *2021*, 3115; c) J. García-Álvarez, E. Hevia, V. Capriati, *Chem. Eur. J.* **2018**, *24*, 14854–14863. d)

[12] S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti, C. Prandi, *Chem. Commun.* **2019**, *55*, 7741-7744.

[13] D. Arnodo, S. Ghinato, S. Nejrotti, M. Blangetti, C. Prandi, *Chem. Commun.* **2020**, *56*, 2391-2394.

[14] S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2021**, *27*, 2868-2874.

[15] U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta, V. Pace, *ChemSusChem* **2019**, *12*, 40-70.

[16] F. R. Leroux, J. Mortier, in *Arene Chemistry* (Ed.: J. Mortier), John Wiley & Sons, Inc., Hoboken, New Jersey, **2015**, pp. 741-776.

[17] a) F. F. Mulks, L. J. Bole, L. Davin, A. Hernan-Gomez, A. Kennedy, J. Garcia-Alvarez, E. Hevia, *Angew. Chem. Int. Ed.* **2020**, *59*, 19021-19026; *Angew. Chem.* **2020**, *132*, 19183-19188; b) D. Elorriaga, B. Parra-Cadenas, A. Antiñolo, F. Carrillo-Hermosilla, J. García-Álvarez, *Green Chem.* **2022**, *24*, 800-812.

[18] M. Fairley, L. J. Bole, F. F. Mulks, L. Main, A. R. Kennedy, C. T. O'Hara, J. Garcia-Alvarez, E. Hevia, *Chem. Sci.* **2020**, *11*, 6500-6509.

[19] L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Sci.* **2016**, *7*, 1192-1199.

[20] V. Pace, L. Castoldi, A. R. Alcántara, W. Holzer, *Green Chem.* **2012**, *14*, 1859-1863.

[21] J. Clayden, Y. J. Y. Foricher, H. K. Lam, *Eur. J. Org. Chem.* **2002**, *2002*, 3558-3565.

[22] However, metalation of *N*,*N*-dimethyl analogue **1c** with LiTMP was ineffective yielding exclusively S_NAc derived products.

[23] Treatment of **2d** with *s*-BuLi (2 eq.) afforded salicylamide **3a** as the sole product due to the extremely fast competitive halogen-lithium exchange

[24] S.-i. Mohri, M. Stefinovic, V. Snieckus, *J. Org. Chem.* **1997**, *62*, 7072-7073.

[25] Low regioselectivity has been observed performing the metalation of **2s** with *s*-BuLi/TMEDA in THF at -78°C. See ref [8]

[26] Assessed by metalation-deuteration experiments on **2v** and ^{2}H NMR analysis of the corresponding deuterated derivative. See Supporting Information for details

[27] W. Wang, V. Snieckus, *J. Org. Chem.* **1992**, *57*, 424-426.

[28] A*o*F rearrangement of **2ad** with *s*-BuLi/TMEDA in THF at -78°C led to a regioisomeric 3:2 mixture of amides. See ref [9b]

[29] M. W. Jann, *Pharmacotherapy* **2000**, *20*, 1-12.

[30] A. V. Kalinin, M. A. J. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. L. Coelho, M. Kerr, V. Snieckus, *Synlett* **1997**, *1997*, 839-841.

[31] C.-W. Chang, R.-J. Chein, *J. Org. Chem.* **2011**, *76*, 4154-4157.

[32] X.-D. Qin, Z.-J. Dong, J.-K. Liu, L.-M. Yang, R.-R. Wang, Y.-T. Zheng, Y. Lu, Y.-S. Wu, Q.-T. Zheng, *Helv. Chim. Acta* **2006**, *89*, 127-133.