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Solvent-controlled, chemodivergent oxidative anionic Fries rearrangement of *O*-aryl carbamates under aerobic conditions

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We disclose herein a mild and efficient organolithium-mediated protocol which enables the chemodivergent transformation of *ortho*-cresol-derived *O*-aryl carbamates into diverse molecular structures by simply changing the nature of the reaction medium, working under air and at room temperature. The use of the biobased 2-MeTHF as solvent allows the chemoselective preparation of α-hydroxy arylacetamides in a single synthetic operation with a remarkable functional group tolerance. Our strategy, which exploits the presence of molecular oxygen arising from the use of bench-type aerobic conditions, relies on a one-pot anionic *homo*-Fries rearrangement/amide enolate autoxidation sequence with two consecutive C–C/C–O bond formation events occurring at the same carbon atom. Furthermore, we also describe the successful use of protic and bioinspired Deep Eutectic Solvents (DESs) as an effective tool to tune the chemoselectivity of the proposed transformation. The fast internal protonolysis of the anion solution, operated by the protic reaction medium, results in an interrupted metalation/rearrangement sequence, enabling the chemoselective preparation of arylacetamides under bench-type aerobic conditions owing to the efficient suppression of the oxidation step.

Introduction

The α-hydroxy amide function is of utmost importance in several areas of organic chemistry owing to its widespread occurrence in agrochemicals and pharmaceuticals with diversified biological targets.[1] In this framework, a recurrent motif in bioactive molecules is the α-hydroxy arylacetamide skeleton, the amide derivative of the naturally occurring mandelic acid, which represents a key building block in both the development of novel drug candidates and the production of fine chemicals (Fig. 1A).[2] Hence, the development of new bench-stable reagents and effective methodologies for the chemoselective preparation of α-hydroxy arylacetamide derivatives using cheap and readily available synthons is of remarkable synthetic value. Besides the traditional approaches based on the amidation of α-hydroxy acids[3] or the reduction of α-keto amides,[4] several *de novo* synthetic methods relying on the assembly of novel C–C bonds have been developed (Fig. 1B), including the nucleophilic homologation of aldehydes by carbamoyl anions,[5] multicomponent approaches with isocyanides[6] or difluorocarbenes,[7] and the base-promoted anionic [1,2]-rearrangement of *O*-benzyl carbamates.[8] A more powerful approach towards mandelic acid amides relies on the α-hydroxylation of arylacetamides by means of a selective C(sp^3)–O bond formation. Excellent indirect strategies have been developed, including the chemoselective α-oxyamination of electrophilically activated arylacetamides promoted by TEMPO[9] and the anionic [2,3]-rearrangement of *O*-functionalized hydroxamic acids.[10] Direct methods based on the aerobic oxidation of C(sp^3)–H bonds are of particular interest, as molecular oxygen is an inexpensive and ubiquitous reagent, and its exploitation in synthetic protocols (rather than its depletion) is of high value also from a sustainability point of view.[11] In this context, the direct aerobic α-hydroxylation of arylacetamides (or α-aryllactams) has been accomplished by means of transition metal-promoted,[12] organocatalytic,[13] and base-promoted[14] approaches (Fig. 1B). However, oxygen-mediated processes frequently suffer from both low selectivity and undesired over-oxidation or degradation pathways.[15] In this context, opportunities for the preparation of α-hydroxy arylacetamides might also arise from the oxidation of nucleophilic polar *s*-block organometallic reagents, a well-established reaction typically promoted by metal oxenoids (hydroperoxide metal salts)[16] or occurring by autoxidation of the organometallic species in the presence of triplet molecular oxygen[17] (Fig. 1C). Despite the enormous progress in this area, especially in the oxidation of aryllithium compounds[18] and enolates,[19] the use of molecular oxygen for the α-hydroxylation

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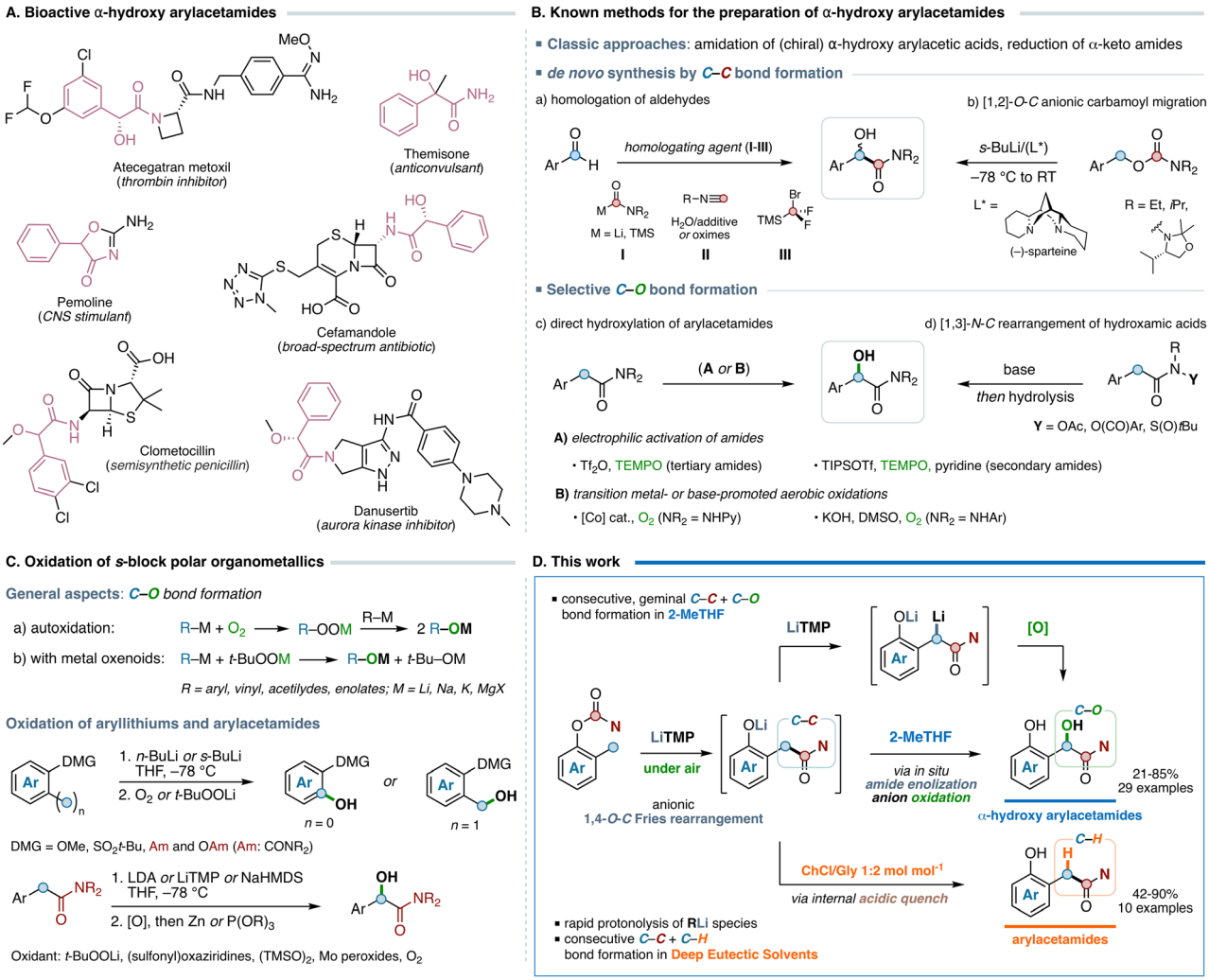

Fig. 1 (A and B) State of the art in the synthesis of α-hydroxy arylacetamides. (C) General overview of the oxidation of organometallic reagents and (D) aim of this work.

of alkali-metal amide enolates has been barely investigated.[20] Recent advancements in the chemistry of *s*-block organometallic compounds have clearly established that transformations involving organolithium, Grignard, and organosodium reagents could be efficiently performed under "bench-type" conditions, working at room temperature in the presence of air, using non-dried sustainable reaction media.[21]

Supported by our recent findings on the reactivity of polar organometallic reagents under non-conventional conditions,[22] we envisaged the possibility of designing a streamlined organolithium-mediated strategy to access α-hydroxy arylacetamides which exploits the presence of molecular oxygen in the reaction mixture, arising from the use of bench-type aerobic conditions. We thus herein report a systematic study on the synergistic combination of lithium amides and molecular oxygen to promote the transformation of *ortho*-cresol derived *O*-aryl carbamates into α-hydroxy arylacetamides using a one-pot, tandem anionic 1,4-O–C Fries (*homo*-Fries)[23] rearrangement/oxidation sequence which involves two bond-making events (one C–C and one C–O bond) occurring at the same carbon atom, working under air and at room temperature, using 2-MeTHF as solvent (Fig. 1D). Mechanistic insights revealed that the oxidation of the intermediate lithium amide enolate triggered by molecular oxygen follows a classic autoxidation pathway with a S_N2-type cleavage process. Furthermore, we also describe the successful use of bioinspired Deep Eutectic Solvents (DESs) as an effective tool to tune the chemoselectivity of the proposed transformation. The use of a protic heterogeneous solvent mixture allows the suppression of the oxidation step owing to the fast protonolysis of the organolithium species (Fig. 1D), enabling the chemoselective preparation of arylacetamides[24] under bench-type aerobic conditions.

Results and discussion

Reaction development

We started our investigation on the anionic *homo*-Fries rearrangement/oxidation sequence of *O*-2-tolyl carbamates under bench-type aerobic conditions using the sterically hindered *N*,*N*-

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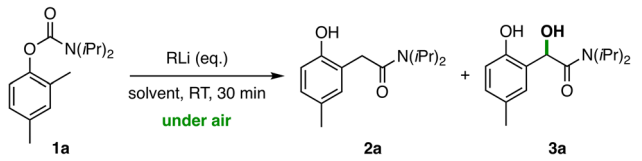
Table 1 Oxidative anionic *homo*-Fries rearrangement of carbamate **1a** under bench-type aerobic conditions[a]



Entry	RLi (eq.)	Solvent	**2a** [b] (%)	**3a** [b] (%)
1	LiTMP (2)	CPME	0	34[c]
2	LiTMP (2)	2-MeTHF	0	54
3	LiTMP (3)	2-MeTHF	0	70[d]
4	LiTMP (3)	4-MeTHP	0	53[e]
5	LiTMP (3)	DME	0	62[e]
6	LiTMP (3)	THF	0	54[e]
7	LiTMP (3)	Et_2O	35	50
8	LiTMP (3)	MTBE	17	48
9	LiTMP (3)	*n*-hexane	32	57
10	LDA (3)	2-MeTHF	0	34
11	*t*-BuLi (3)	2-MeTHF	0	32
12	*s*-BuLi (3)	2-MeTHF	10	36[e,f]

[a] Reaction conditions: **1a** (0.2 mmol), solvent (1 mL), RLi, room temperature (RT), under air (relative humidity = 39%). CPME = cyclopentyl methyl ether, 2-MeTHF = 2-methyltetrahydrofuran, 4-MeTHP = 4-methyltetrahydropyran, DME = 1,2-dimethoxyethane, MTBE = methyl *t*-butyl ether). LiTMP (1 M in 2-MeTHF), LDA (1 M in 2-MeTHF), *t*-BuLi (1.7 M in pentane), *s*-BuLi (1.4 M in cyclohexane). [b] Determined by ^{1}H NMR using *n*-heptane as the internal standard. [c] Unreacted **1a** (64%) was recovered. [d] Yield of isolated **3a** = 68%. [e] The corresponding *N*,*N*-diisopropyl-2-oxoacetamide was also detected in the reaction mixture. See the SI for details. [f] The *ortho*-rearranged salicylamide (45%) was observed in the crude reaction mixture. See ref. 22d.

diisopropyl carbamate **1a** as a model substrate (Table 1). In a preliminary experiment, a solution of compound **1a** (0.2 mmol, 0.2 M) in cyclopentyl methyl ether (CPME) was reacted with a freshly prepared solution of LiTMP (1 M in CPME, 2.0 equiv.) in the absence of an external electrophile, working at room temperature and under air (Table 1, entry 1).[22d] Aqueous quench of the anion solution after 30 min afforded a mixture of unreacted carbamate **1a** (64%) and the arylacetamide **3a** hydroxylated at the benzylic position in 34% yield. The structure was confirmed by NMR spectroscopy and X-ray analysis of **3a**, which crystallised by slow, room temperature evaporation of a chloroform solution into the monoclinic $P2_1/n$ space group.[25] Performing the metalation of **1a** using 2-MeTHF as reaction medium under the same reaction conditions led to a significant increase of the reaction yield of **3a** (54%), alongside the formation of unidentified byproducts (entry 2). Pleasingly, increasing the amount of metalating agent (3 equiv.) resulted in the chemoselective formation of the desired α-hydroxy arylacetamide **3a** in a satisfactory 70% yield (entry 3). The use of higher amounts of LiTMP or, alternatively, longer reaction times had a detrimental effect on the reaction yield due to the partial over-oxidation of **3a** to the corresponding α-ketoamide byproduct (see the SI for details). Similar results were obtained when the reaction was performed using either the emerging eco-friendly alternative 4-MeTHP (entry 4) or other ethereal solvents with high coordinating ability for organolithiums, such as 1,2-dimethoxyethane (DME, entry 5) and tetrahydrofuran (THF, entry 6). While the use of less coordinating solvents had no effect on the anionic rearrangement, a significant impact on the oxidation step was observed as demonstrated by the considerable amount of unoxidized **2a** (17–35%) detected in the reaction mixture (entries 7–9). By contrast, treatment of carbamate **1a** with the less basic and sterically hindered lithium amide LDA (entry 10) resulted in a significant decrease of the reaction yield (34%). Analogously, the use of common alkyllithium compounds was less effective, resulting in a loss of selectivity due to the formation of *ortho*-Fries (*s*-BuLi)[22d] or several unidentified byproducts (*t*-BuLi) in non-negligible amounts (entries 11 and 12). Noteworthy, the stability of the organolithium species in 2-MeTHF is remarkable under these bench-type aerobic conditions. Performing the reaction on **1a** in 2-MeTHF either under a dry Ar/O_2 atmosphere or in the presence of humidified air (82% RH) provided comparable yields of **3a** (71% and 69%, respectively) to those obtained with a standard bench-type (open air) experimental setup (39% RH, see the SI for details). These results clearly indicate that almost no protonolysis of the organolithium species occurs under air over the reaction time, owing to the beneficial effect of the highly hydrophobic 2-MeTHF on the stability of lithium amides.[22b,26] Consequently, the reaction could be performed even at high moisture levels without significantly affecting the reaction yield.

Scope of the reaction

With optimized reaction conditions in hand (Table 1, entry 3), the scope and limitations of this transformation were evaluated for a series of functionalized *O*-aryl carbamates **1** bearing different substituents at both the *O*-aryl ring and the amine moiety, using the commodity metalating agent LiTMP in 2-MeTHF under air. The anionic Fries rearrangement of *O*-aryl *N*,*N*-diisopropylcarbamates **1a–q** proceeded smoothly *en route* to a variety of substituted α-hydroxy arylacetamides bearing neutral (**3a–b**), electron-donating (**3f–i** and **3o**), halogenated (**3c** and **3e**) groups at the aromatic moiety, and polyaromatic rings (**3j–k**) without formation of byproducts arising from competitive directed *ortho*-, remote[27] or *peri*-[28] metalation processes (Scheme 1). Remarkably, the synthesis of compound **3a** has been easily scaled up to 4.0 mmol of carbamate **1a** (1 g) with comparable efficiency in terms of yield and selectivity (66% *versus* 68% on a small scale, see the SI). Pleasingly, our methodology also tolerates the presence of common organolithium-sensitive functional groups, allowing the chemoselective preparation of several polyfunctionalized α-hydroxy arylacetamides without competitive pathways, such as X/Li exchange (**3d**), transmetalation (**3l**), carbolithiation (**3m–n**) or α-lithiation (**3h** and **3p**) reactions. Treatment of carbamate **1q**, prepared from the *ortho*-methyl derivative of eugenol, with LiTMP gave access to the corresponding polysubstituted α-hydroxy arylacetamide **3q**, albeit in a modest 34% yield. Other sterically hindered *O*-tolyl carbamates derived from secondary (cyclo)alkyl (**1s–1aa**) and aryl (**1ab–ac**) amines performed as well, thereby delivering a series of α-hydroxylated tertiary acetamides **3s–ad** in good

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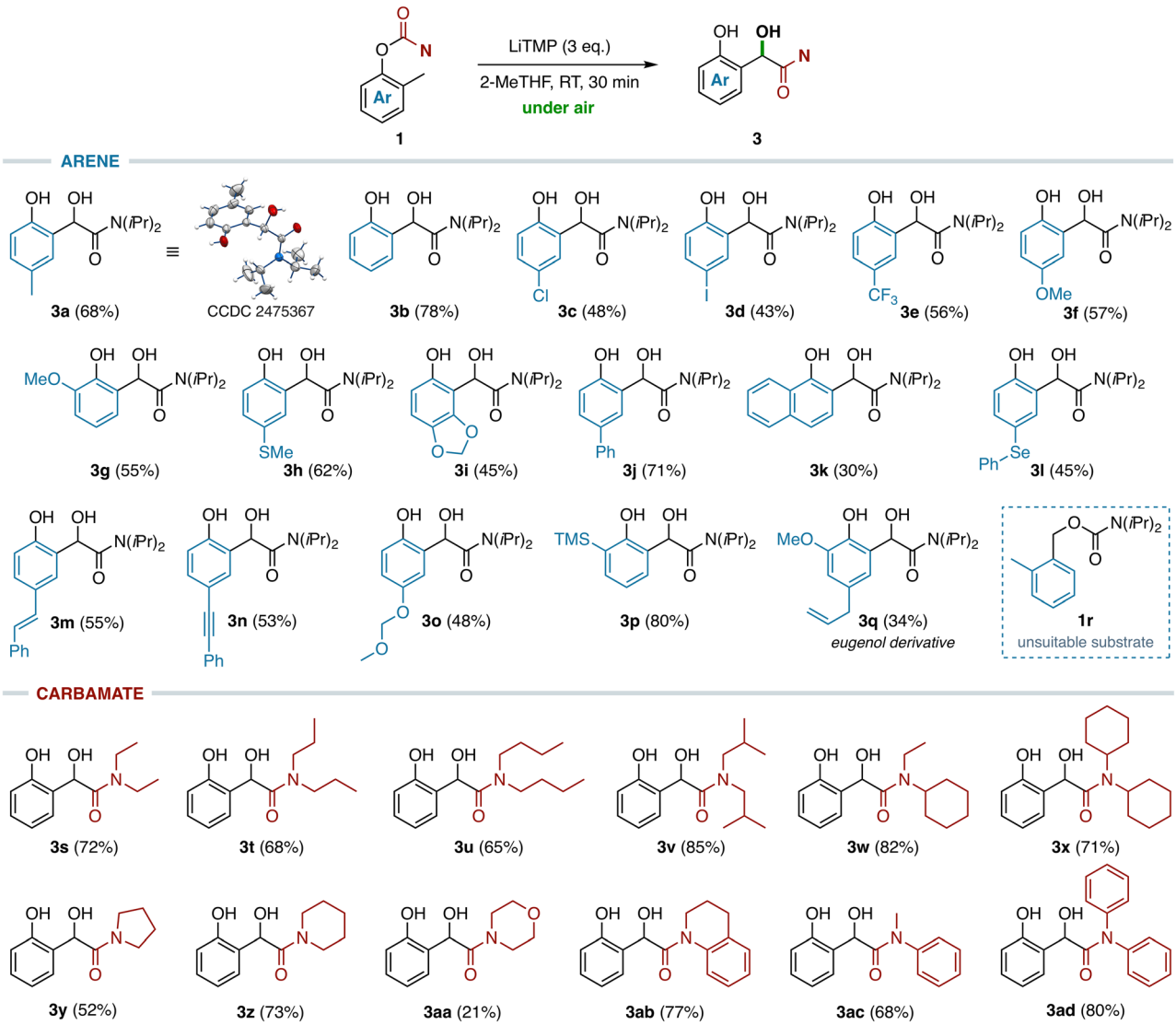

Scheme 1 Scope of the oxidative *homo*-Fries rearrangement of *O*-aryl carbamates **1**. Reaction conditions: **1** (0.2 mmol, 0.2 M in 2-MeTHF), LiTMP (1 M in 2-MeTHF, 3 equiv.), room temperature (RT), under air. Reported yields refer to isolated products.

yields (21–85%). By contrast, when the reaction was performed on carbamate **1r** the sole [1,2]-carbamoyl migration product, arising from the competitive α-lithiation at the *O*-benzylic position,[8b] was recovered in 88% yield (see the SI). Similarly, attempts to extend our methodology to 2-ethylphenol derivatives were unsuccessful. Treatment of the *N*,*N*-diisopropyl carbamate of 2-ethylphenol under optimized reaction conditions resulted in a partial anionic *homo*-Fries rearrangement[29] which afforded the corresponding non-oxidized arylacetamide in 36% yield (alongside 52% of unreacted starting material), whereas no oxidation products were detected in the reaction mixture (see the SI).

Mechanistic investigations

To gain more mechanistic insights into the anionic *homo*-Fries rearrangement/oxidation sequence, additional control experiments were performed (Scheme 2A). Carbamate **1a** was treated with LiTMP (3 equiv.) under an inert atmosphere (Ar), using dry and thoroughly degassed 2-MeTHF as solvent. Under these conditions, the sole arylacetamide **2a** arising from the benzylic metalation/anionic Fries rearrangement was isolated in 73% yield, confirming the effective role of molecular oxygen as the oxidant in the reaction sequence.[30] Additionally, electrophilic quenching with deuterium of the anion solution generated by metalation of **1a** with LiTMP under air yielded compound **2a-D** with good deuterium incorporation (73% D) at the benzylic position after only 10 s of metalation, resulting from a fast enolization process occurring after the carbamoyl migration step. Taken together, these results confirmed that our developed protocol, which allows the chemoselective conversion of *O*-aryl carbamates to α-hydroxy arylacetamides in a single synthetic operation, exploits both a cascade of LiTMP-mediated transformations and the presence of molecular oxygen arising from the use of bench-type conditions.

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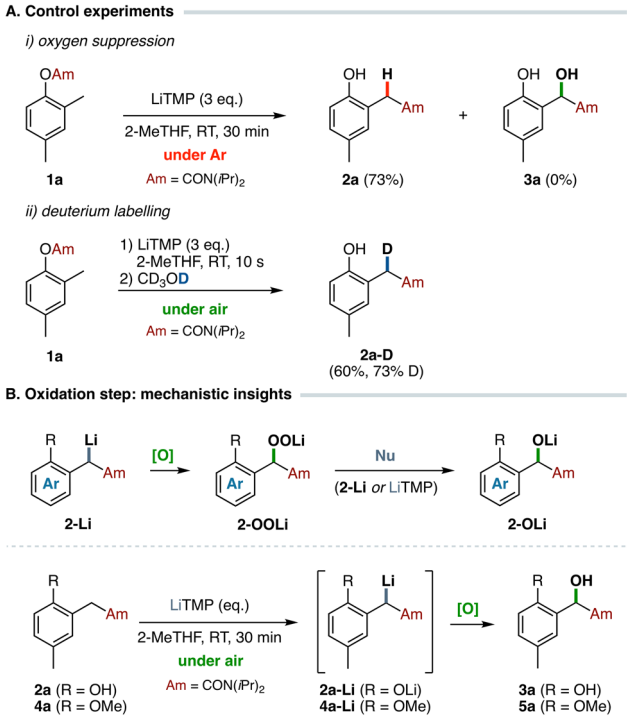

entry	substrate	LiTMP (eq.)	Product (Yield %)[a]	
1	**2a**	1	**2a** (81)	**3a** (6)
2	**2a**	2	**2a** (3)	**3a** (60)
3	**4a**	1	**4a** (30)	**5a** (45)
4	**4a**	2	**4a** (0)	**5a** (63)

Scheme 2 (A) Control experiments on *O*-aryl carbamate **1a**. Reaction conditions: **1a** (0.2 mmol, 0.2 M in 2-MeTHF), LiTMP (1 M in 2-MeTHF, 3 equiv.), room temperature (RT). (i) Reaction was performed under an Ar atmosphere. (ii) Reaction was performed under air. CD_3OD (5 eq.) was added after 10 s. Reported yields refer to isolated products. D incorporations are based on ^{1}H NMR integration and confirmed with ^{2}H NMR. (B) Mechanistic insights into the oxidation step. Reaction conditions: **2a** or **4a** (0.2 mmol, 0.2 M in 2-MeTHF), LiTMP (1 M in 2-MeTHF), room temperature (RT), under air. [a] Determined by ^{1}H NMR using *n*-heptane as the internal standard.

Further mechanistic investigations were subsequently devoted to the oxidation step. The nature of the species involved in the aerobic oxidation of organolithium compounds by molecular oxygen has been clearly established, and oxenoid-type compounds were often proposed as intermediates. The cleavage of the intermediate lithium peroxide is often rationalized by the fast interaction of the electrophilic lithium peroxide with a second molecule of non-oxidized organolithium to form the corresponding lithium alkoxide (autoxidation process).[31] In our proposed anionic *homo*-Fries rearrangement/oxidation sequence, we speculated that the cleavage of the intermediate lithium peroxide **2-OOLi** could be performed either by the non-oxidized amide enolate **2-Li** (autoxidation) or, alternatively, by the excess of lithium amide LiTMP (Scheme 2B). The latter should account for the required three equivalents of metalating agent (one for each metalation step and an additional equivalent for the cleavage of **2-OOLi** species) to achieve a satisfactory yield of hydroxylated acetamide **3**, as emerged from the optimization studies (see Table 1, entry 3). Hence, additional experiments were performed on arylacetamide **2a** to elucidate the nature of the species involved in the nucleophilic cleavage of the intermediate peroxide **2-OOLi** generated during the oxidation step (Scheme 2B). As expected, treatment of **2a** with a stoichiometric amount of LiTMP (1 equiv.) was ineffective in promoting the oxidation due to the protonolysis of the metalating agent by the more acidic phenolic hydroxy group, leading to the exclusive formation of the corresponding lithium phenoxide and the consequent recovery of unreacted **2a** upon acidic quench (Scheme 2B, entry 1). By contrast, the use of a two-fold amount of LiTMP resulted in the complete α-hydroxylation of **2a** owing the effective aerobic oxidation of amide enolate **2a-Li**, generated in turn by the additional equivalent of metalating agent (entry 2). These findings strongly suggest a classic autoxidation pathway promoted by the non-oxidized **2a-Li**, rather than a LiTMP-induced cleavage of the intermediate oxenoid-type species which should theoretically afford an equimolar mixture of **2a**:**3a**. Interestingly, a similar result was observed upon metalation of the anisole-derived acetamide **4a** with a stoichiometric amount of LiTMP (1 equiv.), which afforded an almost 1 : 1 mixture of unreacted **4a** and α-hydroxy arylacetamide **5a** (entry 3). By contrast, complete conversion of **4a** was solely observed in the presence of a two-fold excess of metalating agent (entry 4), suggesting in this case a competitive behaviour of LiTMP as nucleophile *versus* **4a-Li** in the cleavage of the intermediate lithium peroxide.

This experimental evidence has been further investigated by DFT calculations. The reaction free energies involved in the nucleophilic cleavage of model oxenoid-type intermediates, bearing a lithium alkoxide (**2b-OOLi**, **A**) or a methoxy- (**4b-OOLi**, **C**) substituent at the aromatic ring, operated by either the parent non-oxidized organolithiums **2b-Li**/**4b-Li** (pathway a) or LiTMP (pathway b) have been estimated (Scheme 3a). Computational results disclosed that the cleavage of hydroperoxide salt **2b-OOLi** (**A**, Scheme 3b) by the non-oxidized amide enolate **2b-Li**,[32] according to an established autoxidation pathway which generates two molecules of lithium alkoxide **2b-OLi** (**B**) as products, proceeds through a transition state (**TS I**) in which the key structural element is a six-membered cyclic $(-Li-O-)_3$ core organized into a chair-like conformation. The significant elongation of the O–O bond (from 1.43 Å in **2b-OOLi** to 1.75 Å in **TS I**), and the almost linear alignment of the former **2b-Li** nucleophilic carbon with the electrophilic oxygen in **TS I** (C_{Li}–O–O angle = 16.3°), strongly suggest a S_N2-type process involved in the cleavage of hydroperoxide salt **2b-OOLi**.[33] The relatively low cleavage barrier of the O–O bond (estimated $\Delta G^{\ddagger}$ = 23.7 kcal mol^{-1}), and the significant thermodynamic stability of the resulting lithium alkoxide with respect to the starting reactants, further corroborate the hypothesis that a classic autoxidation process of amide enolate **2b-Li** occurs in the presence of molecular oxygen. Conversely, the interaction of **2b-OOLi** with the lithium amide LiTMP (Scheme 3b), which should produce the lithium alkoxide **2b-OLi** (**B**) and the *N*-hydroxy TMP lithium salt ($TMPO^-Li^+$) species, was significantly disfavoured due to the high free energy barrier required for the heterolytic O–O bond cleavage (estimated $\Delta G^{\ddagger}$ = 99.3 kcal mol^{-1}), arising from

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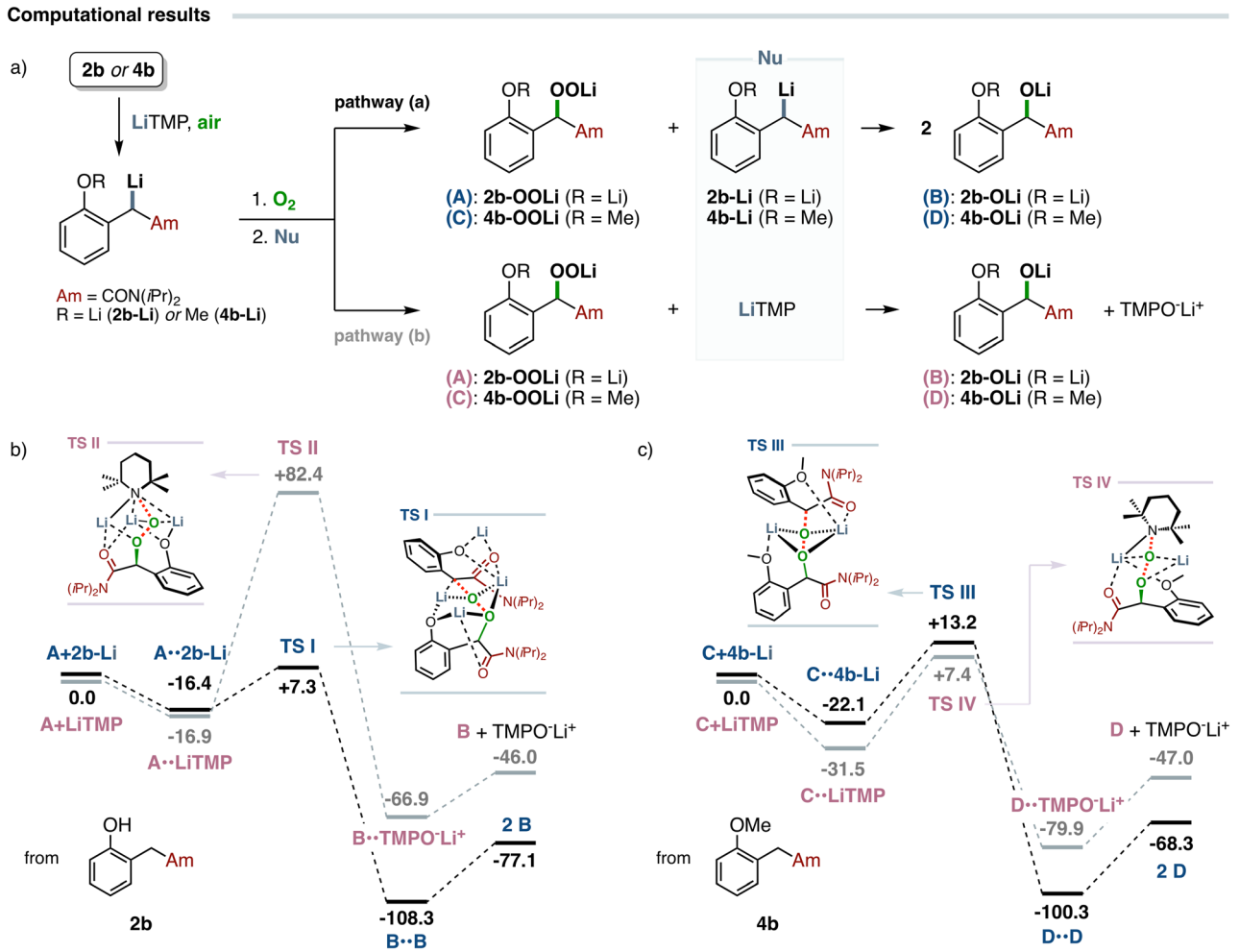

Scheme 3 (a) Proposed nucleophilic cleavage pathways involved in the oxidation step. (b and c) Gibbs free energy profiles (kcal mol^{-1}, at 298 K) estimated by density functional theory (DFT) calculations for the nucleophilic cleavage of (b) **2b-OOLi** and (c) **4b-OOLi** species. Red dotted lines in TS I-IV represent breaking and forming bonds. Calculations were performed at the M06-2X/def2-TZVP//M06-2X/def2-SVP level; see the SI for details.

the formation of a more sterically crowded and less organized transition state (**TS II**). As emerged from the calculations, the computed geometry of **TS II** clearly discourages a nucleophilic cleavage pathway on **2b-OOLi** operated by LiTMP (O–O = 1.40 Å, N_{Li}–O–O angle = 101.0°).

A different scenario emerged from computational investigations on the oxidation of the metalated anisole-derived arylacetamide **4b** (Scheme 3c). In close analogy to the phenoxide-derived intermediate **2b-OOLi**, the nucleophilic cleavage of the hydroperoxide salt **4b-OOLi** (**C**) operated by the unoxidized amide enolate **4b-Li** proceeds through the formation of an organized heterodimeric transition state (**TS III**) containing a bent four-membered (–Li–O–)$_2$ cyclic core (estimated $\Delta G^{\ddagger}$ = 35.3 kcal mol^{-1}). Interestingly, in this case the exergonic O–O bond cleavage of the electrophilic **4b-OOLi** by LiTMP proceeds *via* the formation of a relatively more stable transition state **TS IV** (−5.8 kcal mol^{-1} *versus* **TS III**) with a comparable free energy barrier (estimated $\Delta G^{\ddagger}$ = 38.9 kcal mol^{-1}). The geometries of both TSs, showing comparable O–O bond distances (1.73 Å and 1.74 Å for **TS III** and **TS IV**, respectively) and an almost linear orientation of the nucleophile with the peroxide moiety (C_{Li}–O–O = 19.2°, **TS III** and N_{Li}–O–O = 10.5°, **TS IV**), were in good accordance with those involved in a S_N2 cleavage process. Overall, these simulations disclosed that in the presence of a lithium alkoxide group on the aromatic ring (arising from the preliminary anionic Fries rearrangement step) the oxidation of the lithium amide enolate follows a classic autoxidation pathway, where the intermediate hydroperoxide salt interacts with the non-oxidized enolate to yield two molecules of the corresponding lithium alkoxide.[34] In contrast, in the absence of a complementary anionic site at the aromatic ring (*e.g.* in the case of arylacetamides **4a–b**) the analysis of the free energy barriers indicates that the lithium amide strongly competes against the amide enolate (or is privileged) in the nucleophilic cleavage of the electrophilic peroxide. These findings are in good agreement with the experimental results (see Scheme 2B), where the complete oxidation of arylacetamides **2a** (R = OLi) and **4a** (R = OMe) has been achieved in the presence of one (**2a**,

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entry 2, autoxidation pathway) or two (**4a**, entry 4) equivalents of metalating agent, respectively.

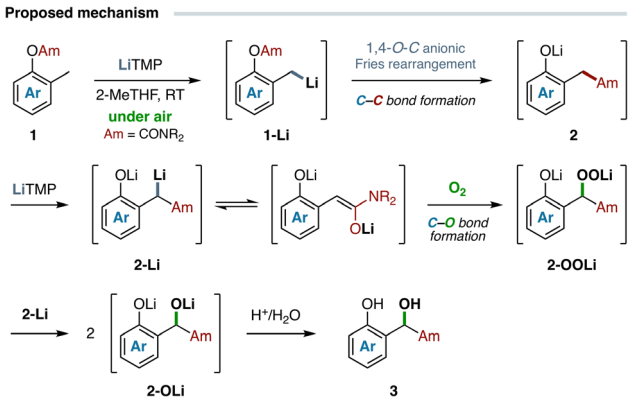
Hence, we are inclined to propose the initial benzylic metalation of carbamate **1**, followed by a fast anionic 1,4-*O*-*C* Fries rearrangement, to form the corresponding intermediate arylacetamide **2**, which is promptly enolized by the excess of metalating agent (Scheme 4).[35] The resulting **2-Li** species then undergoes a spontaneous autoxidation process to deliver the α-hydroxy arylacetamide **3** upon protonolysis of the corresponding alkoxide **2-OLi**, generated *in situ* from the nucleophilic cleavage of the intermediate oxenoid species **2-OOLi** by the unoxidized amide enolate **2-Li**. Altogether, four synthetic steps are involved in the aerobic tandem protocol developed herein: the regioselective lateral (benzylic) lithiation, an anionic carbamoyl migration, a chemoselective lithiation α to amide carbonyl, and the autoxidation of the resulting amide enolate promoted by oxygen. This allows, overall, the consecutive formation of a C–C and a C–O bond at the same carbon atom in a single synthetic operation.

Interrupted anionic Fries rearrangement in deep eutectic solvents

Whereas we have shown that the presence of atmospheric molecular oxygen in the reaction mixture, a commonly detrimental species for organolithium-promoted transformations, could be efficiently exploited to assemble hydroxylated acetamide-based structural motifs, final considerations have been devoted to the possibility of suppressing the anion oxidation step while maintaining the use of bench-type aerobic conditions.

Deuterium labelling experiments performed on carbamate **1a** (see Scheme 2A) suggest that the first steps of the reaction sequence (anionic Fries rearrangement and enolization) are faster than the oxidation process, as demonstrated by the relatively high deuterium incorporation in the arylacetamide **2a** observed after only 10 s. Kinetic studies of the reaction, using the model carbamate **1a** (0.2 mmol) as a substrate in 2-MeTHF (1 mL), revealed the classic profile of a sequential transformation (Fig. 2). During the initial stage of the reaction the oxidation product **3a** was not formed. Subsequently, a slow consumption of **2a** occurred with the concomitant steady production of **3a** over 30 min. A comparison of the observed rate constants (k_1 and k_2)[36] confirmed that the oxidation of the amide enolate is the rate determining step of the consecutive process.

Consequently, the different kinetics of these two steps could be exploited to perform a rapid quench of the reaction mixture before the oxidation occurs. The rapid protonolysis of the anion solution (*e.g.* by performing an external acidic quench) represents the most intuitive and immediate route to avoid the oxidation of the enolized arylacetamide; however this approach could lack reproducibility due to the short reaction times involved. An alternative and more intriguing possibility is offered by the use of protic Deep Eutectic Solvents (DESs), mixtures of specific hydrogen bond donors (HBDs) and acceptors (HBAs) combined in eutectic molar ratios with peculiar physical properties, high biodegradability and biocompatibility.[37] Several studies have disclosed the ability of protic DESs to promote the kinetic activation of highly polar *s*-block organometallic reagents and, consequently, to improve both the reaction time and the chemoselectivity of several organometallic-mediated transformations without the need for external additives.[38] Overall, the activating effect of DESs facilitates the reactivity of air-sensitive RLi and RMgX species in a protic and aerobic environment over the competitive protonolysis process, which usually becomes predominant after short reaction times.[39] Hence, we envisaged that a combination of the intrinsic properties of protic DESs (acidity and activating effect on organolithiums) with the fast kinetics of the anionic Fries rearrangement step at room temperature could be efficiently exploited to perform *in situ* a rapid quench of the organolithium species in solution generated



Scheme 4 Proposed reaction mechanism based on experimental data and estimated reaction free energies.

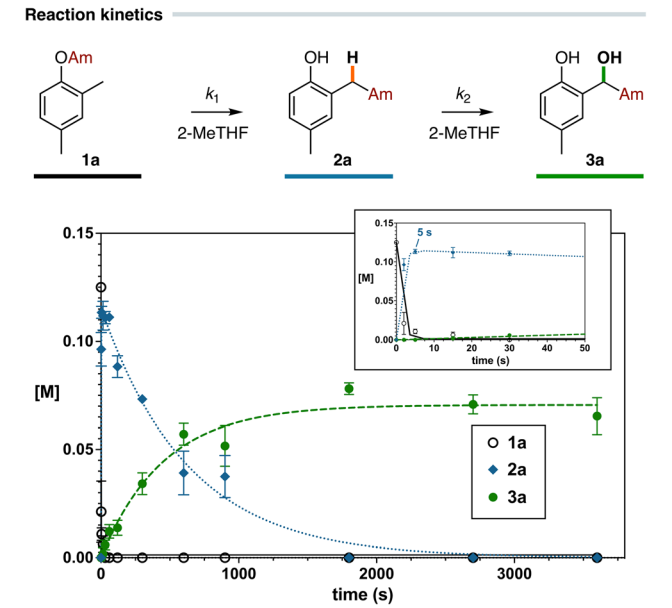


Fig. 2 Plots of **1a**, **2a** and **3a** concentrations [M] *versus* time (s) for the metalation of carbamate **1a** (0.2 mmol, Am=CON(*i*Pr)$_2$) with LiTMP (0.6 mmol, 1 M in 2-MeTHF) at 25 °C, under air. The curves represent unweighted least-squares fits. 2-MeTHF (0.125 M) was used as solvent. $k_1 = 1.1 \pm 0.1\ s^{-1}$; $k_2 = (1.9 \pm 0.5) \times 10^{-3}\ s^{-1}$. Inset: expansion of the reaction profile after 50 s.

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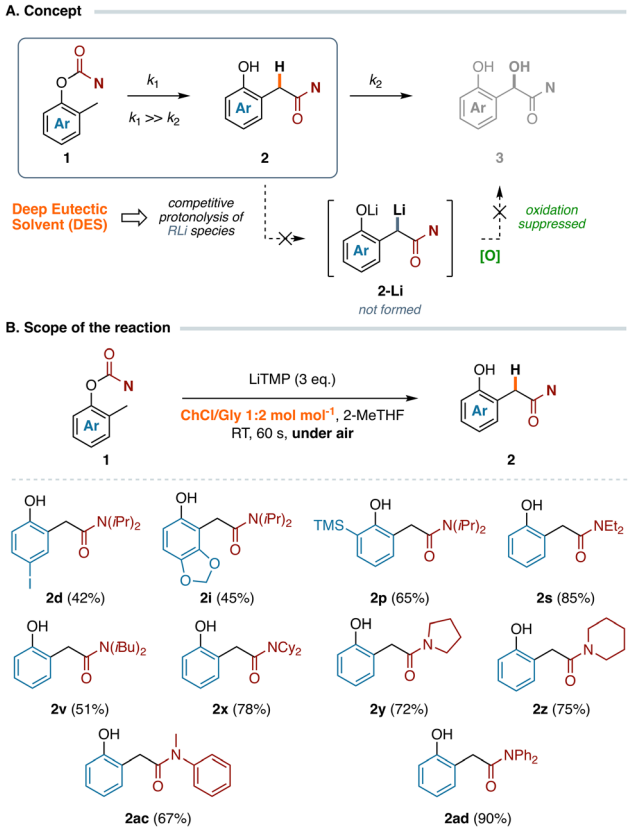

Scheme 5 (A) Programmed Deep Eutectic Solvent-driven strategy to suppress the oxidation step. (B) Scope of the aerobic *homo*-Fries rearrangement of *O*-aryl carbamates **1** in Deep Eutectic Solvent. Reaction conditions: **1** (0.2 mmol, 1 M in 2-MeTHF), ChCl/Gly 1 : 2 mol mol^{-1} (1 g), LiTMP (1 M in 2-MeTHF, 0.6 mmol), 60 s, room temperature, under air. Reported yields refer to isolated products.

upon the metalation/carbamoyl migration process, namely the excess of LiTMP and the amide enolates **2-Li.** In principle, this would suppress the formation of the corresponding α-hydroxylated compounds **3**, allowing the preparation of arylacetamides **2** in a chemoselective fashion working under bench-type aerobic conditions (Scheme 5A). A series of carbamates **1** (0.2 mmol, 1 M in 2-MeTHF), differently substituted at both the aromatic ring and the amide nitrogen, were thus treated with LiTMP (3 equiv.) using a choline chloride (ChCl)/glycerol (Gly) 1 : 2 mol mol^{-1} deep eutectic mixture as the reaction medium (1 g), under air at RT and with vigorous stirring (Scheme 5B).[40]

Pleasingly, under heterogeneous conditions the rearrangement products **2** were exclusively formed within only 60 s in good yields (42–90%), and the corresponding oxidation compounds **3** have never been observed even after a longer reaction time (0.5 h) owing to the efficient protonolysis of the organolithium species by the protic deep eutectic mixture. As expected, when carbamate **1a** (0.2 mmol, 1 M in 2-MeTHF) was treated with LiTMP (0.6 mmol) under heterogeneous aerobic conditions, using the ChCl/Gly 1 : 2 mol mol^{-1} deep eutectic mixture as solvent, the kinetic profile of the reaction lacked the formation of the oxidation product, and a fast conversion of **1a** into the rearranged arylacetamide **2a** was observed ($k_1 = 3.0 \pm 0.8$ s^{-1}, see the SI).

Conclusions

In summary, we have developed a general and efficient organolithium-mediated protocol which exploits the presence of molecular oxygen, a commonly detrimental species in the chemistry of polar *s*-block organometallic reagents, to build polysubstituted scaffolds of remarkable synthetic value in a single synthetic operation. Our methodology enables the transformation of *O*-aryl carbamates into α-hydroxy arylacetamides by resorting to a one-pot, tandem sequence of C–C and C–O bond formation events occurring at the same carbon atom, working under air and at room temperature, using the biobased 2-MeTHF as solvent. Our strategy allows a significant increase in the structural complexity of a simple molecular skeleton with remarkable functional group tolerance while suppressing the formation of overoxidation products without the need for external additives. Furthermore, we have shown that the use of a protic heterogeneous solvent mixture represents an effective tool to tune the chemoselectivity of the proposed transformation. The fast internal protonolysis of the anion solution operated by the protic reaction medium results in the efficient suppression of the oxidation step, enabling the chemoselective preparation of arylacetamides in an aerobic environment as a result of an interrupted metalation/rearrangement sequence. Overall, our strategy allows for the generation of diverse molecular structures in a chemodivergent fashion by simply changing the nature of the reaction medium, thus enlarging the portfolio of organolithium-mediated transformations under non-conventional conditions. The development of other consecutive anionic migration strategies under bench-type aerobic conditions are under investigation and will be reported in due course.

Author contributions

Riccardo Gnavi (methodology, investigation, visualization, writing review and editing); Federica De Nardi and Carolina Meazzo (methodology, investigation, writing review and editing); Simone Ghinato (methodology, investigation); Ettore Grimaldi (investigation); Andrea Maranzana (investigation, software, formal analysis, writing review and editing); Cristina Prandi (supervision, funding acquisition, writing review and editing); and Marco Blangetti (conceptualization, funding acquisition, project administration, supervision, visualization, formal analysis, writing – original draft, writing – review and editing). All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC deposition number 2475367 contains the supplementary crystallographic data for this paper.[25]

The data underlying this study are available in the published article and its supplementary information (SI). Supplementary

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information: general procedures, experimental details, characterization data for both new and known compounds, copies of ^{1}H, ^{13}C, ^{19}F and ^{2}H NMR spectra, and computational details. See DOI: https://doi.org/10.1039/d5sc09227b.

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