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O-Aryl carbamates of 2-substituted piperidines: anionic Fries rearrangement and kinetic resolution by lithiation

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Piperidines and their 2-substituted derivatives are fundamental intermediates for the development of new active pharmaceutical ingredients with improved pharmacokinetic profiles and unique three-dimensional properties. Consequently, the design of synthetic methodologies for their selective transformations into highly valuable scaffolds, aimed at increasing the molecular diversity, is of high importance. We disclose herein a general and efficient organolithium-mediated protocol to promote chemo- and regioselective anionic Fries rearrangement or kinetic resolution processes starting from *O*-aryl carbamates of 2-substituted piperidines. The use of *t*-BuLi allows a regioselective *ortho*-metalation of the *O*-aryl carbamate followed by an intramolecular carbamoyl migration, thereby delivering a series of functionalized *N*-piperidinyl salicylamides in yields of 33 to 95%. The protocol has been successfully extended to 5- and 7-membered saturated N-heterocyclic scaffolds with comparable yields and selectivity. Mechanistic aspects and studies on the use of bench-type aerobic conditions are also detailed. In addition, the chiral *n*-BuLi/(+)-sparteine complex promotes the kinetic resolution of the *O*-aryl carbamate by regioselective lithiation at the 2-position of the piperidine ring. Upon electrophilic quench, the enantioenriched starting material is recovered with a good level of stereoselectivity (up to 85 : 15 er).

Introduction

Nitrogen-based heterocycles are of fundamental importance in several areas of organic chemistry owing both to their widespread occurrence in agrochemical[1] and natural products,[2] and to their remarkable pharmacological properties.[3] In particular, five- and six-membered saturated azacycles substituted in the 2-position are key pharmacophores targeting several biological receptors, including neurokinin (NK1) receptors,[4] poly (ADP-ribose) polymerase (PARP),[5] ion channels,[6] κ-opioid[7] and NTRK[8] receptors, among others.[9] Of these, 2-substituted piperidines are of utmost importance in drug discovery as they allow the development of new active pharmaceutical ingredients with high molecular diversity, unique three-dimensional properties and, consequently, improved pharmacokinetic profiles and bioavailability (Fig. 1A).[10] Hence, the development of methodologies for the assembly of these recurrent structural motifs, with complementary control of the stereocentre at the 2-position, is of high synthetic value.[11] Several routes towards enantioenriched 2-substituted piperidines have been reported (Fig. 1B), mostly relying on the direct α-functionalization of the piperidine core.[12] Other strategies, including the asymmetric hydrogenation of pyridine derivatives,[13] *de novo* synthetic methodologies[14] and enzymatic approaches[15] have also been reported. Among these methods, an attractive possibility is offered by the kinetic resolution (KR) of racemic *N*-Boc protected 2-arylpiperidines by asymmetric lithiation using a chiral *n*-BuLi/sparteine (sp) complex (Fig. 1C).[16] The *N*-Boc protecting group allows high yields of benzylic lithiation due to the fast interconversion of rotamers by rotation around the N–CO bond even at −78 °C, and the resulting organolithiums have shown to be configurationally stable up to −50 °C.[17] This approach allows, upon electrophilic quench of the resulting chiral organolithiums, the recovery of both the unreacted starting material and the quenched product with high levels of enantiopurity.

Whereas the selective kinetic resolution by lithiation of *N*-Boc protected five- and six-membered 2-arylazacycles has been clearly established,[18] the general reactivity of their parent *N*-acyl derivatives remains essentially unexplored.[19] By contrast, we envisioned that *O*-aryl carbamates of 2-substituted piperidines could be suitable platforms for developing

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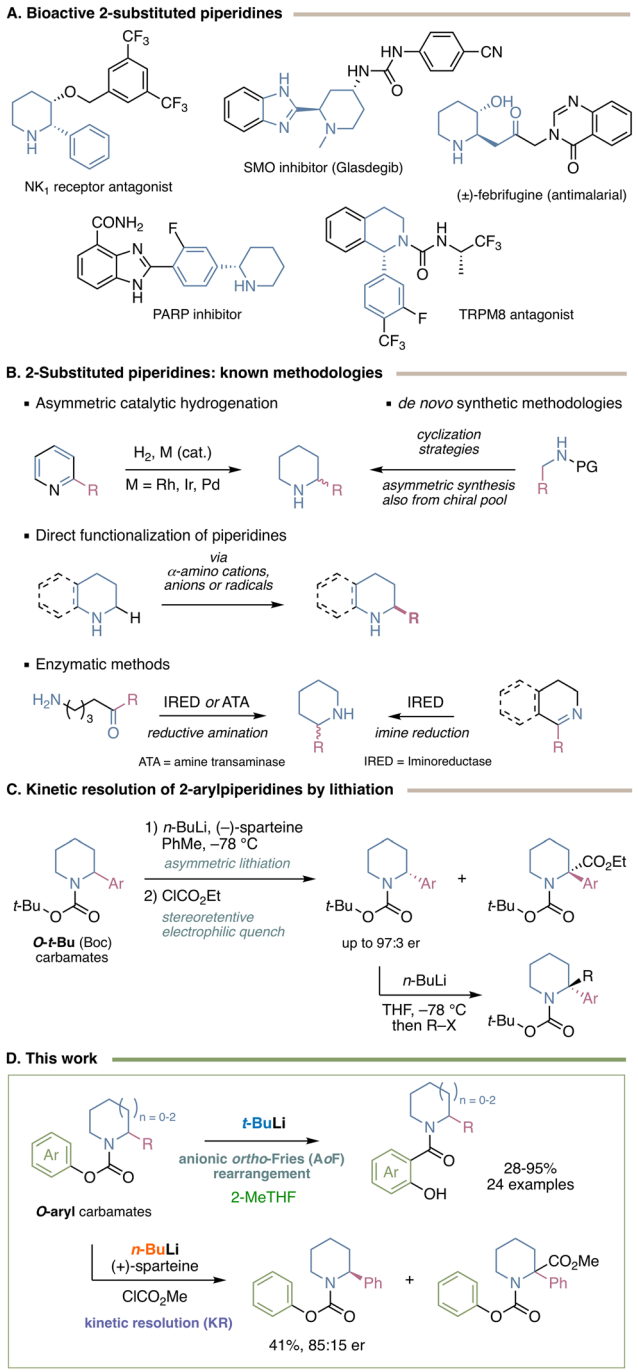


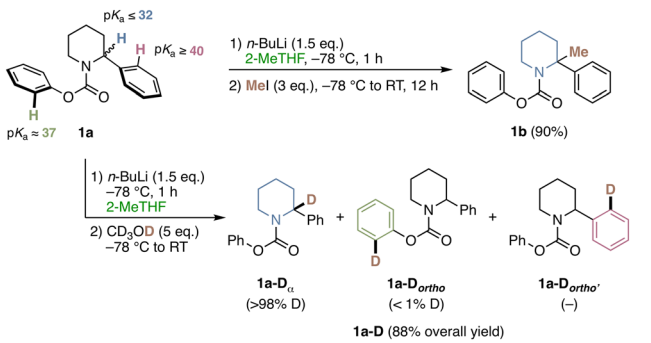
Fig. 1 (A–C) State of the art of 2-substituted piperidines in synthesis and (D) aim of this work.

chemodivergent transformations promoted by organolithium reagents. Indeed, the presence of different metalation sites potentially offers the possibility to perform both an intramolecular carbamoyl migration triggered by a regioselective *ortho*-metalation of the phenolic ring, and a kinetic resolution by lithiation then electrophilic quench upon a regioselective benzylic metalation (Fig. 1D). Hence, the development of a regioselective lithiation strategy should result in the chemodivergent synthesis of both salicylamide derivatives, arising from an anionic *ortho*-Fries rearrangement (A*o*F) reaction, and enantioenriched 2-substituted piperidines bearing tertiary or quaternary stereocentres by means of a kinetic resolution approach. On the basis of these considerations and motivated by our ongoing interest in the development of new *s*-block polar organometallic reagent-mediated transformations,[20] we herein report a systematic study on the usefulness of organolithium reagents to promote chemoselective A*o*F rearrangement or kinetic resolution processes starting from *O*-aryl carbamates of 2-substituted piperidines (Fig. 1D). Our optimized protocol allows for the generation of diverse molecular structures in a chemodivergent fashion by simply changing the nature of the metalating agent, resorting to regioselective metalations of the carbamates with either *t*-BuLi, using the biobased 2-MeTHF as reaction medium, or *n*-BuLi, followed by internal (A*o*F) or external (KR) electrophilic quench of the resulting anionic species.

Results and discussion

Anionic Fries rearrangement

We started our investigation on the metalation/anionic Fries rearrangement of N-heterocyclic *O*-aryl carbamates using the *N*-benzoyl 2-phenylpiperidine **1a** as a model substrate (Scheme 1). This scaffold is particularly interesting, as it presents three potential metalation sites with different relative acidities:[21] (a) the aromatic *ortho*-positions of the phenol ring ($pK_a \approx 37$), whose regioselective abstraction is required to promote an *ortho*-Fries rearrangement process, (b) the less acidic aromatic *ortho*-C–H positions of the distal phenyl ring ($pK_a \geq 40$), and (c) the presence of the most acidic benzylic C–H site at the 2-position of the piperidine ring, which could preclude the possibility to promote a carbamoyl migration by the generation of a thermodynamically favoured benzylic anion at this position. Preliminary metalation/deuteration experiments on **1a** effectively revealed that the lithiation α to the piperidine nitrogen is strongly favoured due to the presence of the aryl substituent which increases the stability of the resulting anion



Scheme 1 Metalation and electrophilic quench of carbamate **1a**. D incorporations are based on ^{1}H NMR integration and confirmed with ^{2}H NMR spectroscopy. Reported yields refer to isolated products.

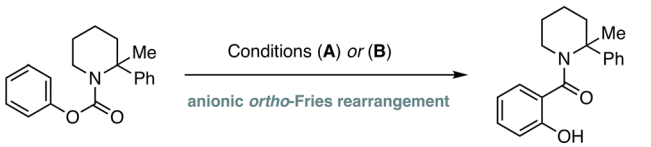
by delocalization. Treatment of carbamate **1a** with *n*-BuLi (1.5 equiv.) at −78 °C using the bio-based and hydrophobic 2-MeTHF as reaction medium, followed by electrophilic quench with CD_3OD after 1 h at −78 °C, afforded an almost quantitative deuterium incorporation at the sole benzylic position α to nitrogen (**1a-D$_\alpha$**), with no detectable amounts of the *ortho*-deuterated species **1a-D$_{ortho}$** and **1a-D$_{ortho'}$** (Scheme 1).

Additionally, even if the competitive α-lithiation could be suppressed, further regioselectivity issues might arise due to the presence of two competitive aromatic rings. The *O*-carbamate moiety is a powerful direct metalation group (DMG) which directs the metalation at the *O*-phenyl ring at −78 °C, with the consequent formation of a 1,3-*O*-*C* carbamoyl migration product (salicylamide) upon warming.[22] On the other side, aminomethyl groups also act as direct metalation groups of aromatic rings, even if a higher temperature for the metalation is typically required.[23] In this case, if lithiation occurs at the piperidine-substituted phenyl ring, a 1,4-*O*-*C* acyl migration process (faster than the 1,3-*O*-*C* rearrangement)[24] should take place upon warming, releasing an *ortho*-piperidinyl benzoate as the final product. Hence, performing the regioselective metalation at a specific aryl ring is of fundamental importance.

To firstly evaluate the feasibility and the regioselectivity of the anionic Fries rearrangement on this class of *O*-aryl carbamates, avoiding the competitive lithiation α to nitrogen, **1a** was converted into the 2,2-disubstituted carbamate **1b** in 90% yield upon metalation with *n*-BuLi (1.5 equiv.) in 2-MeTHF at −78 °C and electrophilic quench with iodomethane (Scheme 1). In a preliminary experiment, treatment of **1b** with 1.5 equiv. of *n*-BuLi at −78 °C in 2-MeTHF successfully promoted the anionic Fries rearrangement upon warming the anion solution to room temperature, affording the rearranged product **2b** in 50% yield (Table 1, entry 1). The regioselectivity of the metalation and the subsequent anionic migration at the *O*-phenyl ring has been determined by NMR spectroscopy and confirmed by the X-ray analysis of **2b**, which crystallised by the slow, room temperature evaporation of a chloroform solution into the monoclinic $P2_1/n$ space group.[25]

No significant improvements have been observed using *s*-BuLi as metalating agent (entry 2), whereas employing the highly basic *t*-BuLi resulted in a cleaner Fries rearrangement, providing the corresponding salicylamide **2b** in a satisfactory 80% yield after 1 h at room temperature (entry 3). Longer rearrangement times led to comparable results, while decreasing the amount of *t*-BuLi to 1.1 equiv. resulted in a considerable decrease of the reaction yield (see Table S1, SI). Employing the mixed-metal systems LIC-KOR (*n*-BuLi/KO*t*-Bu 1 : 1 molar ratio, entry 4)[26] and LiNK (*n*-BuLi/KO*t*-Bu/TMP 1 : 1 : 1 molar ratio, entry 5)[27] as metalating agents provided comparable results to those obtained with *t*-BuLi, and the salicylamide **2b** was produced in 74% and 70% yield, respectively. The sterically hindered LiTMP was also effective to promote the reaction, affording **2b** in a moderate 48% yield (entry 6) which can be further improved to 63% using a three-fold excess of metalating agent (entry 7). In contrast, less basic

Table 1 Anionic *ortho*-Fries rearrangement of carbamate **1b** under different reaction conditions[a]



1b **2b**

Conditions (**A**): RLi (eq.), solvent, −78 °C, 30 min; then −78 °C to RT, 1 h
Conditions (**B**): RLi (eq.), solvent, RT, 60 s, under air

Entry	Conditions	RLi (eq.)	Solvent	**2b** [b] (%)
1	A	*n*-BuLi (1.5)	2-MeTHF	50[c]
2	A	*s*-BuLi (1.5)	2-MeTHF	40
3	A	*t*-BuLi (1.5)	2-MeTHF	80
4	A	LIC-KOR (1.5)[d]	2-MeTHF	74
5	A	LiNK (1.5)[e]	2-MeTHF	70
6	A	LiTMP (1.5)	2-MeTHF	48
7	A	LiTMP (3)	2-MeTHF	63
8	A	MeLi (1.5)	2-MeTHF	—
9	A	LDA (3)	2-MeTHF	—
10	B	LiTMP (3)	CPME	78
11	B	LiTMP (3)	2-MeTHF	76
12	B	LiTMP (3)	4-MeTHP	70

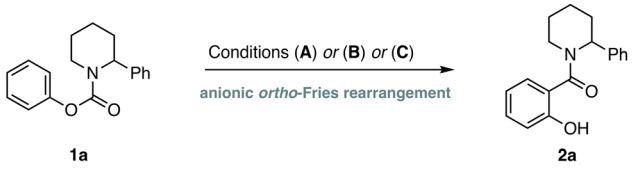
[a] Conditions (A): **1b** (0.2 mmol), RLi, 2-MeTHF (2.0 mL, 0.1 M). *n*-BuLi (2.5 M in hexanes), *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane), MeLi (1.6 M in Et_2O), LiTMP (1.0 M in 2-MeTHF), LDA (1.0 M in 2-MeTHF). Conditions (B): **1b** (0.2 mmol), LiTMP (1.0 M in 2-MeTHF), solvent (2.0 mL, 0.1 M; CPME = cyclopentyl methyl ether, 2-MeTHF = 2-methyltetrahydrofuran, 4-MeTHP = 4-methyltetrahydropyran), under air. [b] Reported yields refer to isolated products. [c] Unreacted **1b** was recovered in 17% yield. [d] LIC-KOR: *n*-BuLi/KO*t*-Bu 1 : 1 molar ratio. [e] LiNK: *n*-BuLi/KO*t*-Bu/TMP(H) 1 : 1 : 1 molar ratio.

organolithiums such as MeLi (entry 8) and LDA (entry 9) were ineffective to promote the Fries rearrangement, and the starting material was recovered unreacted. Based on our previous studies, the D*o*M/A*o*F sequence has also been investigated under bench-type conditions, working under air and at room temperature, and using the hydrophobic ethers (CPME, 2-MeTHF and 4-MeTHP) as reaction media (Table 1, conditions B, entries 10–12). A solution of **1b** (0.2 mmol, 0.1 M) in CPME was thus reacted with a freshly prepared 1 M solution of LiTMP (3 equiv.) in 2-MeTHF, at room temperature and under air (entry 10). Pleasingly, aqueous quench of the reaction mixture after 1 min released the desired salicylamide **2b** in a satisfactory 78% yield. Similar results were obtained using 2-MeTHF (entry 11) and the emerging eco-friendly alternative 4-MeTHP (entry 12), which allowed the isolation of the rearranged product **2b** after 1 min in 76% and 70% yield, respectively. These results clearly confirmed the fast kinetics of both the metalation and the anionic rearrangement steps at room temperature,[20c] and further contribute to enlarge the portfolio of organolithium-mediated protocols under non-conventional conditions.

Once the possibility to promote the anionic *ortho*-Fries rearrangement on this class of sterically hindered N-heterocyclic carbamates had been successfully demonstrated

(Table 1), and the regioselectivity of the metalation had been assessed, we next investigated the feasibility of the *ortho*-metalation and the 1,3-*O*-*C* carbamoyl migration on the *O*-phenyl 2-phenylpiperidine carbamate **1a**. This approach is more intriguing from a synthetic perspective, since (a) the additional synthetic step (α-methylation) aimed at suppressing the highly competitive benzylic lithiation is avoided, and (b) both the racemic substrate and the rearranged product could potentially be subjected to a kinetic resolution process by lithiation. Hence, carbamate **1a** was reacted with a series of organolithium reagents, ranging from highly basic alkyllithiums to less reactive hindered lithium amides, using 2-MeTHF as the environmentally responsible reaction medium under different reaction conditions (Table 2). The use of *s*-BuLi (2 equiv.) as metalating agent in the presence of an equimolar amount of TMEDA was not effective to promote the *ortho*-lithiation of **1a** (entry 1), and the unreacted carbamate **1a** was recovered in 22% yield from a complex reaction mixture. In contrast, treatment of **1a** with a two-fold excess of *t*-BuLi afforded the desired salicylamide **2a** upon warming the anion solution to room temperature, albeit in a modest 45% yield (entry 2). This encouraging result shows that the formation of the *ortho*-anion could be effectively accomplished in the presence of a competitive benzylic position by using an excess of a strong, hindered metalating agent. A slight improvement in **2a** yield (56%) was observed when increasing the metalation time to 2 h (entry 3), whereas using a three-fold excess of *t*-BuLi resulted in the formation of a complex crude reaction mixture (see Table S2, SI). Cognizant that the competitive lithiation α to piperidine nitrogen occurs smoothly also using the less basic *n*-BuLi at −78 °C (Scheme 1), a telescoped double lithiation procedure aimed at increasing the efficiency of the *ortho*-metalation was then investigated. To this purpose, carbamate **1a** was treated with *n*-BuLi (1.5 equiv.) at −78 °C to achieve a quantitative benzylic lithiation and, after 1 h of metalation at this temperature, an equivalent of *t*-BuLi was added at −78 °C to promote the generation of the *ortho*-aryllithium species (entry 4). Upon warming the anion solution to room temperature, aqueous quench of the reaction mixture afforded the rearranged product **2a** in 30% yield. Increasing each metalation time to 2 h led to a significant increase of the reaction yield to 51% (entry 5), however alongside the formation of unidentified byproducts. Pleasingly, when both metalations were performed at −78 °C using a stoichiometric amount of *t*-BuLi (1 equiv.) and the anion solution was warmed to room temperature for 1 h after each lithiation step, the anionic rearrangement proceeded cleanly to afford the rearranged salicylamide **2a** in 71% yield (entry 6). Whereas the use of lithium amides was effective to promote the metalation/anionic rearrangement of 2,2-disubstituted carbamate **1b** (see Table 1), treatment of carbamate **1a** with the less basic and sterically hindered lithium amide LiTMP (3 equiv.) resulted in a significant decrease of the reaction yield (39%) working under classical conditions (entry 7). Furthermore, the use of LiTMP as metalating agent under aerobic conditions, using 2-MeTHF (entry 8) or CPME (entry 9) as solvents, produced the salicylamide **2a** with comparable yields (43% and 30%, respectively), suggesting an overall low efficiency of lithium amides to promote the metalation/rearrangement process on this class of carbamates.[28]

Table 2 Anionic *ortho*-Fries rearrangement of carbamate **1a** under different reaction conditions[a]



1a **2a**

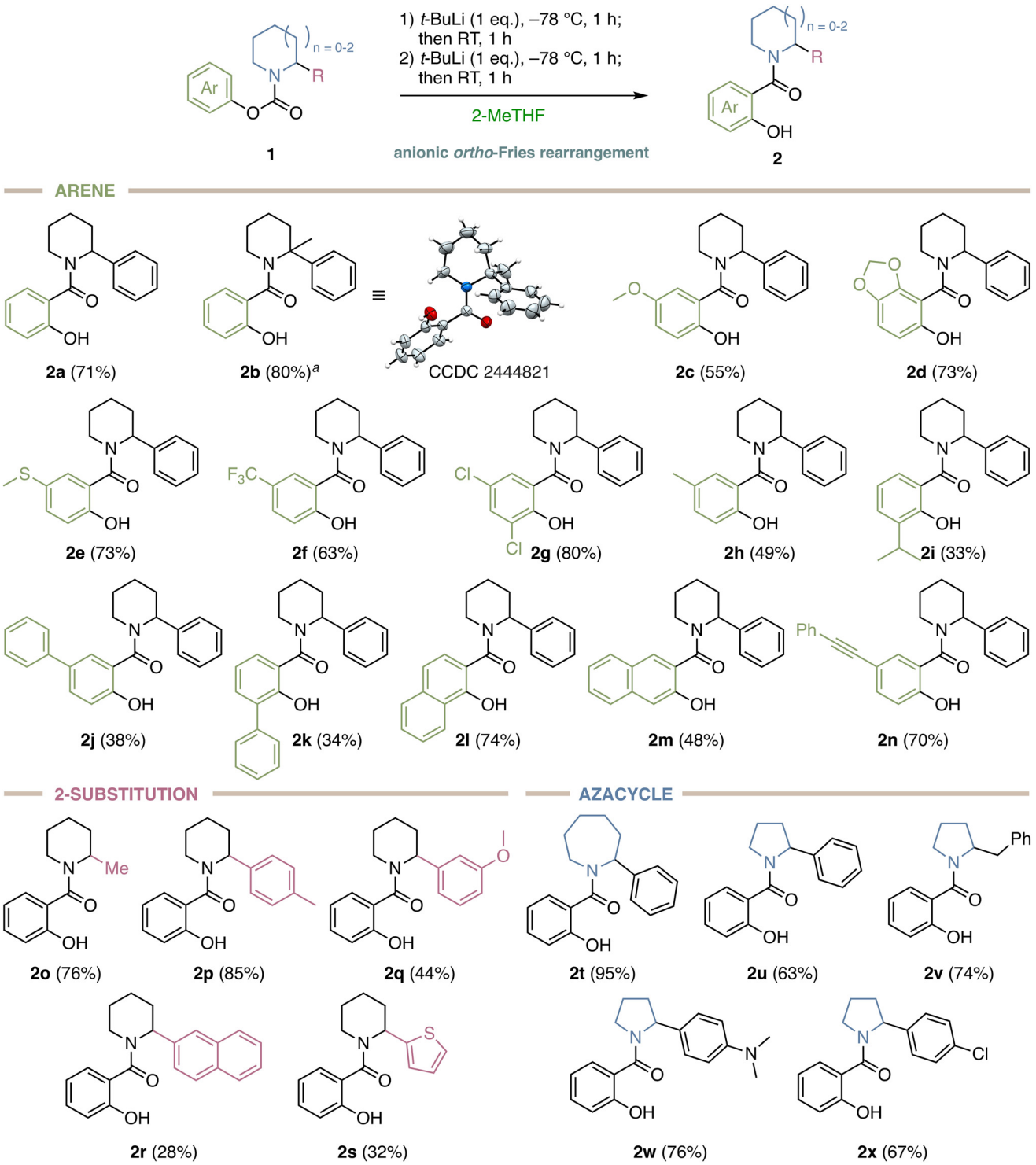
Conditions (**A**): RLi (eq.), 2-MeTHF, −78 °C, time$_1$ (h); then −78 °C to RT, time$_2$ (h)
Conditions (**B**): 1) RLi (eq.), 2-MeTHF, −78 °C, time$_1$ (h)
2) *t*-BuLi (1 eq.), −78 °C, time$_2$ (h); then −78 °C to RT, 1 h
Conditions (**C**): RLi (eq.), 2-MeTHF, RT, time$_1$ (h), under air

Entry	Conditions	RLi (eq.)	Time$_1$ (h)	Time$_2$ (h)	**2a**[b] (%)
1	A	*s*-BuLi (2)[c]	1	1	—[d]
2	A	*t*-BuLi (2)	1	1	45
3	A	*t*-BuLi (2)	2	1	56
4	B	*n*-BuLi (1.5)	1	1	30
5	B	*n*-BuLi (1.5)	2	2	51
6	B	*t*-BuLi (1)	1[e]	1	71
7	A	LiTMP (3)	2	1	39
8	C	LiTMP (3)	0.5	—	43
9	C[f]	LiTMP (3)	0.5	—	30

[a] Conditions (A): **1a** (0.2 mmol), RLi, 2-MeTHF (2.0 mL, 0.1 M). Conditions (B): (1) **1a** (0.2 mmol), RLi, 2-MeTHF (2.0 mL, 0.1 M). (2) *t*-BuLi (1 eq.), 2-MeTHF. *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane), LiTMP (1.0 M in 2-MeTHF). Conditions (C): **1a** (0.2 mmol), LiTMP (1.0 M in 2-MeTHF), 2-MeTHF (2.0 mL, 0.1 M), RT, under air. [b] Reported yields refer to isolated products. [c] An equimolar amount of TMEDA was added. [d] Unreacted **1a** was recovered in 22% yield. [e] After 1 h at −78 °C, the reaction mixture was stirred at RT for 1 h. [f] CPME was used as solvent.

Scope of the reaction

With optimized reaction conditions in hand (Table 2, entry 6), the scope and limitations of this transformation were evaluated for a series of functionalized *O*-carbamates **1** bearing different substituents at both the *O*-aryl ring and the position α to piperidine nitrogen, or different azacycles at the carbamoyl moiety (Scheme 2). Metalation and anionic Fries rearrangement of *O*-aryl 2-phenylpiperidine carbamates **1a–n** proceeded smoothly *en route* to a variety of substituted salicylamides bearing electron-donating (**2c–e**), halogenated (**2f** and **2g**) and neutral (**2h** and **2i**) groups at the *O*-aromatic ring. The A*o*F rearrangement proceeded with satisfactory results also for a series of *O*-polyaromatic 2-phenylpiperidine carbamates, affording the corresponding biphenyl (**2j** and **2k**) and naphthyl (**2l** and **2m**) salicylamides in good yields (34–74%) without formation of byproducts arising from remote-[29] or *peri*-[30]metalation processes. The methodology also tolerates the presence of acetylenic substituents at the aromatic ring (**2n**), although other alkyllithium-sensitive functional groups, such as bromine and olefins, were incompatible with the reaction con-



Scheme 2 Scope of the AoF rearrangement of *O*-aryl carbamates **1**. Reaction conditions: **1** (0.2 mmol, 0.1 M in 2-MeTHF), *t*-BuLi (1.7 M in pentane). Reported yields refer to isolated products. [a] A single addition of *t*-BuLi (1.5 equiv.) was performed as described in Table 1, conditions (A).

ditions, affording complex reaction mixtures or recovery of the starting material after workup.

O-Phenyl carbamates of different α-substituted piperidines provided the corresponding salicylamides **2o–s** in moderate to good yields (28–82%) upon treatment with *t*-BuLi under optimized metalation conditions. Lithiation of carbamate **1o**, bearing a methyl group at the α-position of the piperidine ring, occurred with complete regioselectivity at the *ortho*-position and the yield of the corresponding α-methyl salicylamide **2o** (76%) reflects the efficiency of the *ortho*-lithiation step (see

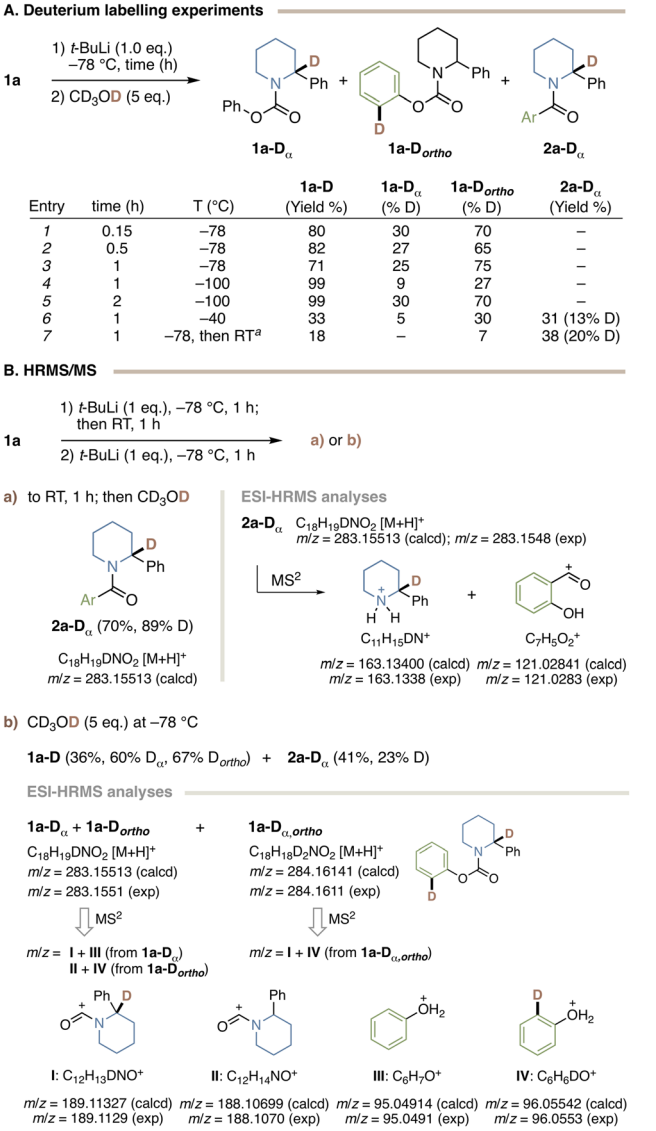
SI for details). The presence of both sterically hindered substituents and/or more acidifying groups at the nitrogen heterocycle seemed to negatively affect the acyl migration, as observed in the case of the carbamates **1r** and **1s**, which gave the corresponding rearranged products **2r** and **2s** in a low 28% and 32% yield, respectively.

An excellent result was obtained using the carbamate of a 7-membered azacycle (**1t**), which afforded the corresponding *N*-acyl 2-phenylazepane **2t** in almost quantitative yield. Other 5-membered azacycles performed as well, thereby releasing a series of *N*-acyl 2-substituted pyrrolidines **2u–x** in good yields, with a good tolerability of different aromatic (**2u** and **2w–x**) and even benzylic (**2v**) substituents at the heterocyclic ring.

Mechanistic investigations

To gain more mechanistic insights into the metalation/rearrangement sequence, additional deuterium labelling experiments were performed (Scheme 3). We first investigated the composition of the reaction mixture over time at different temperatures upon treatment of carbamate **1a** with a stoichiometric amount (1 equiv.) of *t*-BuLi in 2-MeTHF and electrophilic quench with CD_3OD (Scheme 3A). The ^1H and ^2H NMR analyses of the crude reaction mixtures revealed a mixture of **1a-D**$_{ortho}$ (70%) and **1a-D**$_{\alpha}$ (30%) metalation products. These are almost instantaneously formed upon the addition of *t*-BuLi at −78 °C (entry 1), whose ratio did not significantly change over time (entries 2 and 3). The presence of a mixture of monoanionic species has been confirmed by the HRMS analysis of **1a-D** obtained after 1 h of metalation/deuteration at −78 °C, where the sole $[\mathbf{1a\text{-}D} + H]^+$ ion (experimental *m*/*z* = 283.1547) was detected, excluding *a priori* the formation of a dianion upon treatment of **1a** with a stoichiometric amount of *t*-BuLi (see SI).

This preliminary experiment clearly discloses that (a) an increase of temperature is necessary to promote the carbamoyl migration (rearrangement product **2a** was not observed), and (b) no anion equilibration processes occur at low temperature. Performing the metalation at a lower temperature (−100 °C) has no effect on the products ratio, however a longer reaction time (2 h) is required to achieve a satisfactory overall D incorporation (entries 4 and 5). At higher temperature (−40 °C) an almost equimolar mixture of non-rearranged **1a-D** (33%) and salicylamide **2a-D**$_{\alpha}$ (31%, 13% D incorporation at the α-position) was obtained after 1 h of metalation (entry 6). Once the composition of the anions solution at low temperature has been assessed, carbamate **1a** was treated with *t*-BuLi (1 equiv.) in 2-MeTHF at −78 °C, and after 1 h at this temperature, the anion solution was warmed to room temperature (entry 7). Electrophilic quench with deuterium after 12 h afforded a mixture of **2a-D**$_{\alpha}$ and **1a-D**, albeit in low yields (38% and 18%, respectively), whose composition reflects the 7 : 3 ratio of the *ortho*-/α- anions generated at −78 °C. This experimental evidence suggests that (a) no anion equilibration occurs even at room temperature and (b) undesired decomposition side-reactions occur after prolonged reaction times, as confirmed by the low amount of product **2a** isolated from the complex reaction mixture.

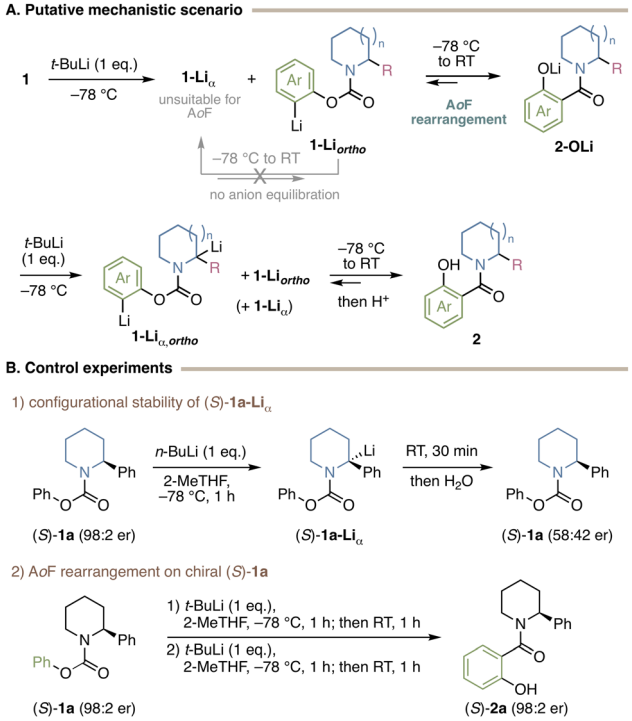


Scheme 3 Mechanistic insights into the metalation/rearrangement of carbamate **1a**. Reaction conditions: **1a** (0.2 mmol, 0.1 M in 2-MeTHF), *t*-BuLi (1.7 M in pentane); then CD_3OD (5 eq.). Reported yields refer to isolated products. D incorporations are based on ^1H NMR integration and confirmed with ^2H NMR. [a] The reaction mixture was stirred at room temperature for 12 h.

Carbamate **1a** was then subjected to a sequential addition of *t*-BuLi, working under optimized reaction conditions, followed by deuteration (Scheme 3B). Hence, **1a** was treated with *t*-BuLi (1 equiv.) at −78 °C followed by warming to room temperature for 1 h, then cooled to −78 °C and treated with a further equivalent of *t*-BuLi. The anion solution was warmed to room temperature for 1 h, and electrophilic quench with CD_3OD produced the sole salicylamide **2a-D**$_{\alpha}$ in 70% yield with a high 89% D incorporation at the α-position, as confirmed by tandem ESI-HRMS analysis

(Scheme 3B, experiment a). Conversely, when the electrophilic quench with deuterium was performed at low temperature (−78 °C) after the second lithiation, a 1 : 1 mixture of **1a-D** (36%) and rearranged product **2a-D$_\alpha$** (41%, 23% D incorporation) was obtained (Scheme 3B, experiment b). Analysis of the ^{1}H and ^{2}H NMR spectra of **1a-D** revealed the 60% D incorporation at the α-(benzylic) position and 67% D incorporation at the *ortho*-position. Tandem HRMS analysis of **1a-D** showed the presence of the expected $C_{18}H_{19}DNO_2$ $[M + H]^+$ adduct ion of m/z = 283.1551 (Δ_{ppm} = 0.04), corresponding to a mixture of monodeuterated species as clearly illustrated by the formation of daughter ions **I–IV** upon fragmentation, arising from the O–(C=O) cleavage of both **1a-D$_\alpha$** (**I** and **III**) and its isotopomer **1a-D$_{ortho}$** (**II** and **IV**). The higher isotopologue with m/z = 284.1611, corresponding to a bis-deuterated $C_{18}H_{18}D_2NO_2$ $[M + H]^+$ adduct ion (Δ_{ppm} = 1.08), has been also detected, whose fragmentation afforded the sole daughter ions **I** and **IV**. Therefore, the presence of the bis-deuterated **1a-D$_{\alpha,ortho}$** compound in the reaction mixture disclosed the formation of the dianionic species **1a-Li$_{\alpha,ortho}$** upon treatment of carbamate **1a** with an excess of *t*-BuLi as metalating agent.

Taken together, these results suggest that in the presence of a stoichiometric amount of metalating agent (1 equiv.) a mixture of regioisomeric **1-Li$_\alpha$** and **1-Li$_{ortho}$** anions is firstly generated at −78 °C and, upon an increase of the reaction temperature, the *ortho*-aryl anion undergoes a partial anionic Fries migration to produce the rearranged salicylamide **2-OLi**, while no equilibration with **1-Li$_\alpha$** occurs (Scheme 4A). The addition of a second equivalent of organolithium promotes the formation of a dianionic species **1-Li$_{\alpha,ortho}$** presumably by an additional *ortho*-metalation of the **1-Li$_\alpha$** species, however in a low amount as confirmed by the D incorporation into the non-rearranged **1a-D** at −78 °C. Whereas also this species could lead to the formation of the same rearranged product **2** upon an increase of the reaction temperature, control experiments using the chiral carbamate (*S*)-**1a** as substrate were performed (Scheme 4B). Since the (*S*)-**1a-Li$_\alpha$** anion, generated by regioselective benzylic lithiation of (*S*)-**1a** with *n*-BuLi at −78 °C, has proven to be configurationally unstable at room temperature,[31] a putative contribution of the (*S*)-**1-Li$_{\alpha,ortho}$** dianion to the formation of salicylamide (*S*)-**2a** should result in a loss of enantiomeric purity of the rearranged product. Hence, the telescoped metalation of enantioenriched (*S*)-**1a** (98 : 2 er) with *t*-BuLi under optimized conditions (−78 °C to room temperature for each lithiation step) was performed and, upon warming the anion solution to room temperature, the corresponding chiral salicylamide (*S*)-**2a** was produced with no loss of enantiopurity. This result strongly suggests that no anionic rearrangement of the dianionic species **1-Li$_{\alpha,ortho}$** occurs, and the resulting salicylamides **2** are produced exclusively by the anionic Fries rearrangement of the **1-Li$_{ortho}$** anion.[32] As a consequence, the regioselectivity of the first lithiation step (and the resulting **1-Li$_{ortho}$: 1-Li$_\alpha$** ratio) determines the maximum yield attainable of salicylamides **2**.

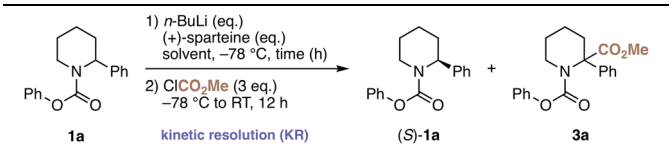


Scheme 4 (A) Proposed reaction mechanism based on experimental data and (B) control experiments on the metalation/rearrangement of enantioenriched carbamate (*S*)-**1a**. Reaction conditions: (*S*)-**1a** (0.2 mmol, 0.1 M in 2-MeTHF), *n*-BuLi (2.5 M in hexanes, 0.2 mmol) or *t*-BuLi (1.7 M in pentane). The enantiomeric ratios were determined by chiral HPLC analysis (see SI).

Kinetic resolution by lithiation

Finally, the kinetic resolution of *O*-phenyl 2-phenylpiperidine carbamate **1a** by lithiation then electrophilic quench was investigated (Table 3). We performed our preliminary asymmetric deprotonation experiments using the non-coordinating toluene as solvent to ensure a slow lithiation and, therefore, a good selectivity.[16c] Hence, *n*-BuLi (0.7 equiv.) was added to a solution containing the carbamate **1a** and (+)-sparteine (0.9 equiv.) in PhMe and, after 3 h of metalation at −78 °C, the electrophilic quench with methyl chloroformate was performed (entry 1). Under these conditions, the unreacted **1a** was recovered in its enantioenriched form (*S*)-**1a** (28% yield) with an acceptable 88 : 12 er. The er was determined by chiral HPLC analysis, and the absolute configuration by comparing the retention time of the major component with the enantiopure carbamate (*S*)-**1a** (see SI). As expected from the previously reported lithiation of *N*-Boc-2-phenylpiperidine,[16c] the chiral base *n*-BuLi/(+)-sparteine can effectively promote a selective asymmetric deprotonation of **1a**, with the (*R*)-**1a** enantiomer preferentially lithiated. However, no selectivity was observed for the product **3a**, which was recovered in 38% yield as racemate. As expected, increasing the amount of both the organolithium and (+)-sparteine resulted in an increased conversion of carbamate **1a**, however with a consistent decrease of the selectivity (entries 2 and 3). The use of *n*-hexane as solvent has

Table 3 Kinetic resolution of carbamate **1a** under different reaction conditions[a]



					(*S*)-**1a**	**3a**
Entry	Solvent	*n*-BuLi (eq.)	(+)-sp (eq.)	Time (h)	% Yield[b] (er)[c]	% Yield[b] (er)[d]
1	PhMe	0.7	0.9	3	28 (88 : 12)	38 (48 : 52)
2	PhMe	0.9	1.1	3	18 (75 : 25)	55 (48 : 52)
3	PhMe	1.8	1.8	3	—	78 (48 : 52)
4	*n*-Hexane	0.7	0.9	3	—[e]	—
5	*n*-Hexane	1.0	1.2	3	21 (24 : 76)	44 (50 : 50)
6	Cumene	0.7	0.9	3.5	59 (63 : 37)	37 (16 : 84)
7	Cumene	0.9	1.1	3.5	18 (69 : 31)	53 (48 : 52)
8	Et_2O	0.7	0.9	1.5	41 (85 : 15)	46 (32 : 68)
9	Et_2O	0.9	1.1	1.5	7 (72 : 28)	88 (49 : 51)
10	CPME	0.7	0.9	2	46 (64 : 36)	31 (30 : 70)

[a] Reaction conditions: **1a** (0.5 mmol), *n*-BuLi (2.5 M in hexanes), (+)-sparteine, solvent (0.1 M), −78 °C; then $ClCO_2Me$ (1.5 mmol). sp = sparteine. [b] Yields refer to isolated products. [c] Determined by chiral HPLC analysis (Chiralpak IB-N5, *n*-heptane/2-propanol 95 : 5, 1 mL min^{-1}; t_R (*R*)-**1a**: 8.2 min, t_R (*S*)-**1a**: 8.8 min). Major component eluted at 8.8 min. [d] Determined by chiral HPLC analysis (Chiralpak IB-N5, *n*-heptane/2-propanol 90 : 10, 1 mL min^{-1}; t_{min}: 9.6 min, t_{maj}: 11.7 min). [e] Unreacted **1a** was quantitatively recovered.

a detrimental effect on the lithiation of **1a** at −78 °C (entry 4), which required the use of a stoichiometric amount of *n*-BuLi/(+)-sparteine. This resulted in a less efficient kinetic resolution of **1a**, affording the enantioenriched (*R*)-**1a** in 21% yield (76 : 24 er) with an unexpected reversal of the selectivity (entry 5). Interestingly, when the lithiation/electrophilic quench process was performed in cumene (entry 6) we observed some loss in selectivity for recovered (*S*)-**1a** (63 : 37 er) and an increased er for product (*R*)-**3a** (84 : 16 er),[33] whereas increasing the amount of chiral base has a detrimental effect on the resolution efficiency (entry 7).

Using the more coordinating diethyl ether as solvent a good resolution of the carbamate **1a** was achieved in a shorter reaction time (entries 8 and 9), and the best results in terms of yield (41%) and er (85 : 15) of (*S*)-**1a** have been obtained using 0.7 equiv. of *n*-BuLi and 0.9 equiv. of (+)-sparteine (entry 8). The highly hydrophobic ether CPME gave similar results to Et_2O in terms of conversion, confirming the similar characteristics between these two solvents in organolithium chemistry.[34] However, a significant loss in selectivity for the recovered **1a** was observed (entry 10). Overall, these results clearly show that the kinetic resolution of the phenyl carbamate (rather than the *tert*-butyl carbamate) of 2-phenylpiperidine **1a** by asymmetric lithiation and electrophilic quench is reasonably feasible using the chiral base *n*-BuLi/(+)-sparteine in several solvents, among which diethyl ether offers the best compromise between yield and selectivity of the enantioenriched (*S*)-**1a** (41%, 85 : 15 er). Conversely, almost no selectivity was observed for the quenched product **3a**, which could be ascribed to a potential stereoinversion of the organolithium intermediate *via* a type of "*conducted tour*" migration of the coordinated $Li^+(S \text{ or } L^*)_n$ ion (S = solvent, L* = (+)-sp) along an almost planar carbanion.[35]

Conclusions

In summary, we have developed a general and efficient organolithium-mediated protocol to promote chemo- and regioselective anionic Fries rearrangement or kinetic resolution processes starting from *O*-aryl carbamates of 2-substituted piperidines. Our methodology allows for the generation of salicylamide derivatives bearing 2-substituted heterocyclic rings at the amide moiety, as the result of an intramolecular carbamoyl migration triggered by the regioselective *ortho*-metalation of the *O*-aryl carbamate with *t*-BuLi, using the biobased 2-MeTHF as sustainable reaction medium. The methodology is wide in scope and could be extended to other 5- and 7-membered *N*-containing heterocycles. Mechanistic insights revealed that a dianionic species is formed in the presence of an excess of *t*-BuLi, alongside an *ortho*-aryllithium-enriched mixture of monoanions, and the resulting salicylamides are produced exclusively by the anionic Fries rearrangement of the **1-Li**$_{ortho}$ anion. Furthermore, bench-type aerobic conditions could also be employed using the sterically hindered LiTMP as metalating agent, thus increasing the portfolio of organolithium-mediated transformations under non-conventional conditions. However, in this case the efficiency of the anionic Fries rearrangement is limited to 2,2-disubstituted piperidines. Furthermore, we have shown that it is possible to promote the kinetic resolution of the racemic *O*-phenyl carbamate of 2-phenylpiperidine by changing the nature of the metalating agent, giving access to chiral piperidine derivatives of high importance in drug discovery and natural products chemistry. Under optimized conditions, the use of the chiral *n*-BuLi/(+)-sparteine complex in diethyl ether allows a regio- and enantioselective deprotonation of the carbamate at the benzylic position, which results in the isolation of the enantioenriched starting material in good yield (41%) and enantiomeric ratio (85 : 15) upon electrophilic quench. The development of other *ortho*-functionalization and kinetic resolution strategies on the salicylamides of 2-substituted piperidines described in this work are under investigation and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its SI: 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 are provided in the SI (PDF). See DOI: https://doi.org/10.1039/d5ob01049g.

CCDC 2444821 contains the supplementary crystallographic data for this paper.[25]

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References

1 C. Lamberth and J. Dinges, in *Bioactive Heterocyclic Compound Classes*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2012, pp. 1–20.

2 B. Gao, B. Yang, X. Feng and C. Li, *Nat. Prod. Rep.*, 2022, **39**, 139–162.

3 (*a*) C. M. Marshall, J. G. Federice, C. N. Bell, P. B. Cox and J. T. Njardarson, *J. Med. Chem.*, 2024, **67**, 11622–11655; (*b*) E. Kabir and M. Uzzaman, *Results Chem.*, 2022, **4**, 100606; (*c*) M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311; (*d*) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.

4 (*a*) R. Di Fabio, G. Alvaro, C. Griffante, D. A. Pizzi, D. Donati, M. Mattioli, Z. Cimarosti, G. Guercio, C. Marchioro, S. Provera, L. Zonzini, D. Montanari, S. Melotto, P. A. Gerrard, D. G. Trist, E. Ratti and M. Corsi, *J. Med. Chem.*, 2011, **54**, 1071–1079; (*b*) G. R. Seabrook, S. L. Shepheard, D. J. Williamson, P. Tyrer, M. Rigby, M. A. Cascieri, T. Harrison, R. J. Hargreaves and R. G. Hill, *Eur. J. Pharmacol.*, 1996, **317**, 129–135.

5 T. D. Penning, G.-D. Zhu, J. Gong, S. Thomas, V. B. Gandhi, X. Liu, Y. Shi, V. Klinghofer, E. F. Johnson, C. H. Park, E. H. Fry, C. K. Donawho, D. J. Frost, F. G. Buchanan, G. T. Bukofzer, L. E. Rodriguez, V. Bontcheva-Diaz, J. J. Bouska, D. J. Osterling, A. M. Olson, K. C. Marsh, Y. Luo and V. L. Giranda, *J. Med. Chem.*, 2010, **53**, 3142–3153.

6 D. B. Horne, N. A. Tamayo, M. D. Bartberger, Y. Bo, J. Clarine, C. D. Davis, V. K. Gore, M. R. Kaller, S. G. Lehto, V. V. Ma, N. Nishimura, T. T. Nguyen, P. Tang, W. Wang, B. D. Youngblood, M. Zhang, N. R. Gavva, H. Monenschein and M. H. Norman, *J. Med. Chem.*, 2014, **57**, 2989–3004.

7 M. E. Schmidt, I. Kezic, V. Popova, R. Melkote, P. Van Der Ark, D. J. Pemberton, G. Mareels, C. M. Canuso, M. Fava and W. C. Drevets, *Neuropsychopharmacology*, 2024, **49**, 1437–1447.

8 (*a*) D. S. Hong, T. M. Bauer, J. J. Lee, A. Dowlati, M. S. Brose, A. F. Farago, M. Taylor, A. T. Shaw, S. Montez, F. Meric-Bernstam, S. Smith, B. B. Tuch, K. Ebata, S. Cruickshank, M. C. Cox, H. A. Burris III and R. C. Doebele, *Ann. Oncol.*, 2019, **30**, 325–331; (*b*) T. W. Laetsch, S. G. DuBois, L. Mascarenhas, B. Turpin, N. Federman, C. M. Albert, R. Nagasubramanian, J. L. Davis, E. Rudzinski, A. M. Feraco, B. B. Tuch, K. T. Ebata, M. Reynolds, S. Smith, S. Cruickshank, M. C. Cox, A. S. Pappo and D. S. Hawkins, *Lancet Oncol.*, 2018, **19**, 705–714.

9 (*a*) T. L. Keller, D. Zocco, M. S. Sundrud, M. Hendrick, M. Edenius, J. Yum, Y.-J. Kim, H.-K. Lee, J. F. Cortese, D. F. Wirth, J. D. Dignam, A. Rao, C.-Y. Yeo, R. Mazitschek and M. Whitman, *Nat. Chem. Biol.*, 2012, **8**, 311–317; (*b*) A. Wolska-Washer and T. Robak, *Future Oncol.*, 2019, **15**, 3219–3232; (*c*) A. D. Elbein, R. Solf, P. R. Dorling and K. Vosbeck, *Proc. Natl. Acad. Sci. U. S. A.*, 1981, **78**, 7393–7397.

10 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930.

11 (*a*) R. Balaji, A. J. David and A. Das, *Asian J. Org. Chem.*, 2024, **13**, e202400257; (*b*) S. D. Griggs, D. T. Tape and P. A. Clarke, *Org. Biomol. Chem.*, 2018, **16**, 6620–6633.

12 (*a*) K. Kasten, N. Seling and P. O'Brien, in *Organic Reactions*, John Wiley & Sons, Inc., 2019, pp. 255–328; (*b*) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel and B. U. W. Maes, *Chem. – Eur. J.*, 2012, **18**, 10092–10142.

13 (*a*) M. Renom-Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari and L. Lefort, *Adv. Synth. Catal.*, 2016, **358**, 2589–2593; (*b*) B. Qu, H. P. R. Mangunuru, X. Wei, K. R. Fandrick, J.-N. Desrosiers, J. D. Sieber, D. Kurouski, N. Haddad, L. P. Samankumara, H. Lee, J. Savoie, S. Ma, N. Grinberg, M. Sarvestani, N. K. Yee, J. J. Song and C. H. Senanayake, *Org. Lett.*, 2016, **18**, 4920–4923; (*c*) M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 12761–12764; (*d*) Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2012, **51**, 10181–10184; (*e*) F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 2850–2852; (*f*) C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966–8967.

14 (*a*) F. Alkhathami, L. Y. Chieng, Y. Ortin, M. Rubini and P. Evans, *Eur. J. Org. Chem.*, 2025, e202400886; (*b*) C. Shan, J. Xu, L. Cao, C. Liang, R. Cheng, X. Yao, M. Sun and J. Ye, *Org. Lett.*, 2022, **24**, 3205–3210; (*c*) P. Fischer, M. Morris, H. Müller-Bunz and P. Evans, *Eur. J. Org. Chem.*, 2020, 1165–1176; (*d*) G. Zhao, D. P. Canterbury, A. P. Taylor, X. Cheng, P. Mikochik, S. W. Bagley and R. Tong, *Org. Lett.*, 2020, **22**, 458–463; (*e*) X. Ma, I. R. Hazelden, T. Langer,

R. H. Munday and J. F. Bower, *J. Am. Chem. Soc.*, 2019, **141**, 3356–3360; (*f*) R. K. Zaidan and P. Evans, *Eur. J. Org. Chem.*, 2019, 5354–5367; (*g*) M. A. Schafroth, S. M. Rummelt, D. Sarlah and E. M. Carreira, *Org. Lett.*, 2017, **19**, 3235–3238; (*h*) M. Hussain, T. S.-L. Banchelin, H. Andersson, R. Olsson and F. Almqvist, *Org. Lett.*, 2013, **15**, 54–57; (*i*) S. Lebrun, A. Couture, E. Deniau and P. Grandclaudon, *Org. Lett.*, 2007, **9**, 2473–2476.

15 (*a*) D. Arnodo, F. De Nardi, S. Parisotto, E. De Nardo, S. Cananà, F. Salvatico, E. De Marchi, D. Scarpi, M. Blangetti, E. G. Occhiato and C. Prandi, *ChemSusChem*, 2024, **17**, e202301243; (*b*) S. C. Cosgrove, J. I. Ramsden, J. Mangas-Sanchez and N. J. Turner, in *Methodologies in Amine Synthesis*, ed. A. Ricci and L. Bernardi, WILEY-VCH GmbH, Weinheim, Germany, 2021, pp. 243–283.

16 (*a*) A. Choi, A. Das, A. J. H. M. Meijer, I. Proietti Silvestri and I. Coldham, *Org. Biomol. Chem.*, 2024, **22**, 1602–1607; (*b*) A. Choi, A. J. H. M. Meijer, I. P. Silvestri and I. Coldham, *J. Org. Chem.*, 2022, **87**, 8819–8823; (*c*) E. J. Cochrane, D. Leonori, L. A. Hassall and I. Coldham, *Chem. Commun.*, 2014, **50**, 9910–9913.

17 (*a*) T. K. Beng, J. S. Woo and R. E. Gawley, *J. Am. Chem. Soc.*, 2012, **134**, 14764–14771; (*b*) N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien and I. Coldham, *J. Am. Chem. Soc.*, 2012, **134**, 5300–5308.

18 (*a*) S.-H. Yeo, A. Choi, S. Greaves, A. J. H. M. Meijer, I. P. Silvestri and I. Coldham, *Chem. – Eur. J.*, 2023, **29**, e202300815; (*b*) A. Das, A. Choi and I. Coldham, *Org. Lett.*, 2023, **25**, 987–991; (*c*) A. El-Tunsi, N. Carter, S.-H. Yeo, J. D. Priest, A. Choi, C. M. Kobras, S. Ndlovu, I. Proietti Silvestri, A. K. Fenton and I. Coldham, *Synthesis*, 2021, 355–368; (*d*) A. Choi, A. El-Tunsi, Y. Wang, A. J. H. M. Meijer, J. Li, X. Li, I. Proietti Silvestri and I. Coldham, *Chem. – Eur. J.*, 2021, **27**, 11670–11675; (*e*) R. A. Talk, A. El-Tunsi, C. C. Robertson and I. Coldham, *Eur. J. Org. Chem.*, 2019, 5294–5301; (*f*) N. Carter, X. Li, L. Reavey, A. J. H. M. Meijer and I. Coldham, *Chem. Sci.*, 2018, **9**, 1352–1357.

19 (*a*) J. P. Lutz, S. T. Chau and A. G. Doyle, *Chem. Sci.*, 2016, **7**, 4105–4109; (*b*) N. Assimomytis, Y. Sariyannis, G. Stavropoulos, P. G. Tsoungas, G. Varvounis and P. Cordopatis, *Synlett*, 2009, 2777–2782.

20 (*a*) F. Marra, F. De Nardi, F. Rossi, E. Priola, C. Prandi and M. Blangetti, *Eur. J. Org. Chem.*, 2024, e202400313; (*b*) S. Ghinato, C. Meazzo, F. De Nardi, A. Maranzana, M. Blangetti and C. Prandi, *Org. Lett.*, 2023, **25**, 3904–3909; (*c*) S. Ghinato, F. De Nardi, P. Bolzoni, A. Antenucci, M. Blangetti and C. Prandi, *Chem. – Eur. J.*, 2022, **28**, e202201154; (*d*) S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti and C. Prandi, *Chem. – Eur. J.*, 2021, **27**, 2868–2874; (*e*) D. Arnodo, S. Ghinato, S. Nejrotti, M. Blangetti and C. Prandi, *Chem. Commun.*, 2020, **56**, 2391–2394; (*f*) S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti and C. Prandi, *Chem. Commun.*, 2019, **55**, 7741–7744.

21 R. R. Fraser, M. Bresse and T. S. Mansour, *J. Am. Chem. Soc.*, 1983, **105**, 7790–7791.

22 R. D. Jansen-van Vuuren, S. Liu, M. A. J. Miah, J. Cerkovnik, J. Košmrlj and V. Snieckus, *Chem. Rev.*, 2024, **124**, 7731–7828.

23 (*a*) H. W. Gschwend and H. R. Rodriguez, in *Organic Reactions*, John Wiley & Sons, Inc., 2005, pp. 1–360; (*b*) F. N. Jones, R. L. Vaulx and C. R. Hauser, *J. Org. Chem.*, 1963, **28**, 3461–3465; (*c*) F. N. Jones, M. F. Zinn and C. R. Hauser, *J. Org. Chem.*, 1963, **28**, 663–665.

24 H. Kim, K. Inoue and J.-i. Yoshida, *Angew. Chem., Int. Ed.*, 2017, **56**, 7863–7866.

25 CCDC 2444821 (compound **2b**).

26 L. J. Bole and E. Hevia, *Nat. Synth.*, 2022, **1**, 195–202.

27 (*a*) P. Fleming and D. F. O'Shea, *J. Am. Chem. Soc.*, 2011, **133**, 1698–1701; (*b*) M. Blangetti, H. Müller-Bunz and D. F. O'Shea, *Chem. Commun.*, 2013, **49**, 6125–6127; (*c*) M. Blangetti, P. Fleming and D. F. O'Shea, *J. Org. Chem.*, 2012, **77**, 2870–2877.

28 A significant amount of unreacted starting material has always been recovered when LiTMP was used as metalating agent.

29 D. Tilly, J. Magolan and J. Mortier, *Chem. – Eur. J.*, 2012, **18**, 3804–3820.

30 J. Clayden, C. S. Frampton, C. McCarthy and N. Westlund, *Tetrahedron*, 1999, **55**, 14161–14184.

31 For comparison with the configurational stability of the analogue *N*-Boc protected 2-lithio-2-phenylpiperidine see ref. 17.

32 Although **1-Li$_{\alpha}$** and **1-Li$_{\alpha,ortho}$** species do not contribute to the formation of salicylamides **2**, the unreacted starting material has never been recovered upon aqueous quench of the reaction mixture due to a partial competitive nucleophilic cleavage of the carbamate moiety.

33 Based on related chemistry using *N*-Boc-2-phenylpiperidine, we assume that the electrophilic quench occurs with retention of configuration.

34 S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson and V. Pace, *ChemSusChem*, 2019, **12**, 1147–1154.

35 R. Knorr, C. Behringer, J. Ruhdorfer, U. von Roman, E. Lattke and P. Böhrer, *Chem. – Eur. J.*, 2017, **23**, 12861–12869.

