



Cite this: *Chem. Sci.*, 2023, **14**, 10140

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th June 2023
Accepted 26th August 2023

DOI: 10.1039/d3sc03216g
rsc.li/chemical-science

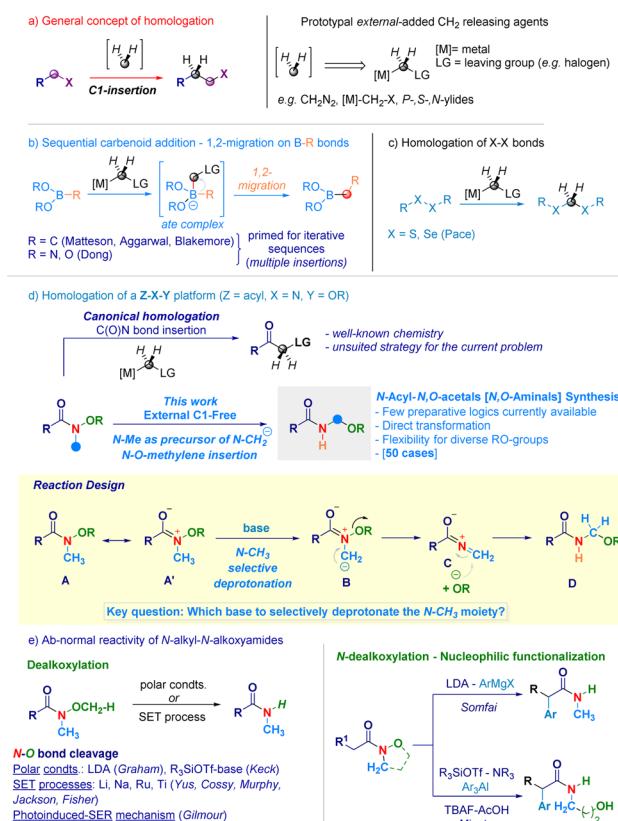
Introduction

Homologation techniques enable the progressive insertion of a constant unit (e.g. $-CH_2-$) within a given chemical bond.¹ These operations are playing nowadays a prominent role in the assembly of complex molecular entities and exhibit a significant potential in guiding the fine-tuning of crucial physical-chemical parameters.² Since the introduction almost one century ago by Arndt and Eistert of the archetypal homologating agent³ – diazomethane (CH_2N_2) –, subsequent studies converged in individuating the $LG-CH_2-[M]$ motif as the general descriptor for C1-releasing agents (Scheme 1a). Mechanistically, the transformation can be represented as the formal delivery of the C1 unit from a donor – externally added – agent to a recipient lynchpin which, through the triggering of 1,2-migration-type events furnishes the homologated skeleton.⁴ The venerable Matteson homologation of boronates with lithium carbenoids (nucleophilic C1-agents, Scheme 1b)⁵ elegantly extended to iterative processes by Aggarwal,⁶ and Blakemore⁷ – well illustrates the controlled insertions into C–B

Base-mediated homologative rearrangement of nitrogen–oxygen bonds of *N*-methyl-*N*-oxyamides†

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Due to the well known reactivity of C(O)–N functionalities towards canonical C1-homologating agents (e.g. carbenoids, diazomethane, ylides), resulting in the extrusion of the *N*-centered fragment *en route* to carbonyl compounds, formal C1-insertions within N–O bonds still remain obscure. Herein, we document the homologative transformation of *N*-methyl-*N*-oxyamides – with high tolerance for diverse O-substituents – into *N*-acyl-*N*,*O*-acetals. Under controlled basic conditions, the *N*-methyl group of the same starting materials acts as a competent precursor of the methylene synthon required for the homologation. The logic is levered on the formation of an electrophilic iminium ion (via N–O heterolysis) susceptible to nucleophilic attack by the alkoxide previously expulsed. The procedure documents genuine chemocontrol and flexibility, as judged by the diversity of substituents placed on both amide and nitrogen lynchpins. The mechanistic rationale was validated through experiments conducted on D-labeled materials which unambiguously attributed the origin of the methylene fragment to the *N*-methyl group of the starting compounds.



Scheme 1 General context of the presented work.

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† Electronic supplementary information (ESI) available. CCDC 2191936. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc03216g>



bonds and served as source of inspiration for the more recent work on N-B and O-B bond homologations by Dong.⁸ In the course of our studies on programmable LiCH_2X -mediated homologation of carbon electrophiles,⁹ we validated the rationale for the selective insertion of methylene units into chalcogenide bonds (S-S and Se-Se analogues) to construct geminal disulfurated methanes (dithioacetal-like – Scheme 1c).¹⁰ One intriguing aspect is whether a C1-insertion could take place selectively on a more sophisticated Z-X-Y platform, where both Z-X and X-Y bonds might undergo homologation (Scheme 1d): to the best of our knowledge, these clusters have not been previously investigated in C1-insertion sequences. In this context, *N*-alkoxy-substituted amides¹¹ constitute representative models since both the C(O)-N and the N-O fragments could be subjected to the methylene insertion: as documented in recent work by our group,¹² amide-type substrates undergo homologation (employing [M]-CH₂-LG reagents) at the C(O)-N linkage – yielding α -substituted ketones^{11b,12c,13} – thus, precluding *de facto* the use of such agents for inserting the C1-unit within the N-O bond (Scheme 1d – up). Beside introducing the concept of N-O homologation, the prospected transformation would provide a modular and rapid approach towards challenging – yet stable¹⁴ – *acyclic N*-acyl-*N,O*-acetals (*i.e.* *N,O*-aminals).¹⁵ Noteworthy, the preparation of these analogues – *i.e.* RN(H)-CH₂-OR¹ motif – has been much less explored compared to methods for assembling substituted congeners and, still remains circumscribed to the electrochemical oxidation of aliphatic amides introduced by Linstead,¹⁶ or to the Katritzky's amidoalkylation of alcohols.¹⁷

In this scenario, we wondered if the homologating element (–CH₂) could be generated from the constitutive *N*-methyl substituent of the *N*-alkoxy amide through a deprotonative event. Accordingly, a *N*-methyl-*N*-methoxyamide^{13a} A represents a pertinent model to make productive the concept: as anticipated, it possesses – as judged by the NC(O) delocalization (A \leftrightarrow A') – relatively acidic *N*-methyl protons amenable to removal with a base of adequate strength. In this circumstance, a ylide-type intermediate B would be formed prior to its collapse – *via* expulsion of the alkoxide – to a terminal, electrophilic iminium ion C,¹⁸ capable of intercepting the same nucleophile (RO[–]) and, thus yielding the homologated adduct D. A series of critical aspects required fine tuning, also in view of the hitherto explored chemistry of the O-CH₃ moiety of Weinreb-like amides functional to access secondary amides (Scheme 1e). In this context, Graham pointed out that under polar conditions – the lithium amide base LDA ($\text{p}K_a = 36$)¹⁹ selectively deprotonates the O-CH₃ group giving a demethoxylated amide (*via* E2 mechanism),²⁰ thus predicting a critical role of the base for generating the requested ylide.²¹ To further complicate this base-mediated scenario, enolizable *N*-alkyl-*N*-alkoxyamides²² can serve as manifolds for sequential *N*-dealkoxylation – nucleophilic functionalization to gather α -substituted amides, as documented by Somfai²³ and Miyata.²⁴ Moreover, N-O breaking operations on *N*-alkyl-*N*-alkoxyamides benefited from adopting (metal) based single electron transfer logics,²⁵ for which Gilmour in 2022 presented an elegant organocatalytic photoinduced alternative (Scheme 1e).²⁶

Despite these precedents on the N-O bond cleavage, the seminal work by Beak²⁷ on the lithiation of *N,N*-dimethylamides supported our initial hypothesis of selectively deprotonate the N-CH₃ fragment. Herein, we report the homologative assembly of *N*-acyl-*N,O*-acetals starting from *N*-alkoxy-*N*-methyl-amides through the use of the same *N*-methyl group of alkoxyamide as a formal C1-delivering agent. Our findings shed light on a novel reactivity – beyond classical acylation and enolate chemistry – of *N*-alkoxyamides in which the C(O)N bond maintains its chemical integrity in a carbanion environment while, the labile N-O linkage (55–65 kcal mol^{–1})^{26,28} undergoes homologation.

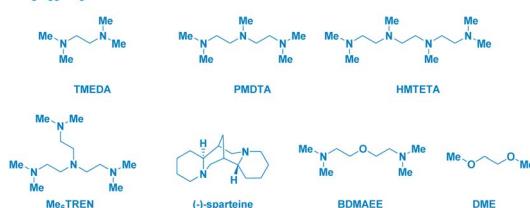
Results and discussion

The enantiomerically pure Weinreb amide **1** generated from the common nonsteroidal anti-inflammatory drug Ibuprofen was chosen as the model substrate (Table 1). Upon treatment with *s*-BuLi in THF at –78 °C (entry 1), the corresponding ketone **2b** – derived from classical Weinreb amide chemistry – was obtained as the unique product (with traces of the demethoxylated

Table 1 Reaction optimization^a

Entry	RLi	Additive (equiv.)	Solvent	Product(s) ^b (%)
1	<i>s</i> BuLi	—	THF	2 (—); 2a (6); 2b (90)
2	<i>s</i> BuLi	TMEDA (1.6)	THF	2 (29); 2a (17); 2b (34)
3	<i>s</i> BuLi	TMEDA (1.6)	Et ₂ O	2 (23); 2a (20); 2b (31)
4	<i>s</i> BuLi	TMEDA (3.2)	THF	2 (30); 2a (24); 2b (27)
5	<i>s</i> BuLi	TMEDA (1.6)	MeTHF	2 (48); 2a (11); 2b (8)
6 ^c	<i>s</i> BuLi	PMDTA (1.6)	MeTHF	2 (81)
7 ^d	<i>s</i> BuLi	PMDTA (1.6)	THF	2 (59); 2a (15); 2b (12)
8 ^e	<i>s</i> BuLi	PMDTA (1.6)	MeTHF	2 (62)
9 ^f	<i>s</i> BuLi	PMDTA (3.2)	MeTHF	2 (64); 2a (15)
10	<i>s</i> BuLi	HMETA (1.6)	MeTHF	2 (43); 2a (22); 2b (30)
11	<i>s</i> BuLi	Me ₆ TREN (1.6)	MeTHF	2 (35); 2a (16); 2b (24)
12	<i>s</i> BuLi	(–)-Spart. (1.6)	MeTHF	2 (51); 2a (23); 2b (18)
13	<i>s</i> BuLi	BDMAEE (1.6)	MeTHF	2 (47); 2a (18); 2b (14)
14	<i>t</i> BuLi	PMDTA (1.6)	MeTHF	2 (36); 2a (15); 2b (21)
15	<i>n</i> BuLi	PMDTA (1.6)	MeTHF	2 (12); 2a (19); 2b (37)
16	LTMP	—	MeTHF	2 (5); 2a (80)
17 ^g	<i>s</i> BuLi	PMDTA (1.6)	MeTHF	2 (46); 2a (8); 2b (10)

Deaggregating additives evaluated

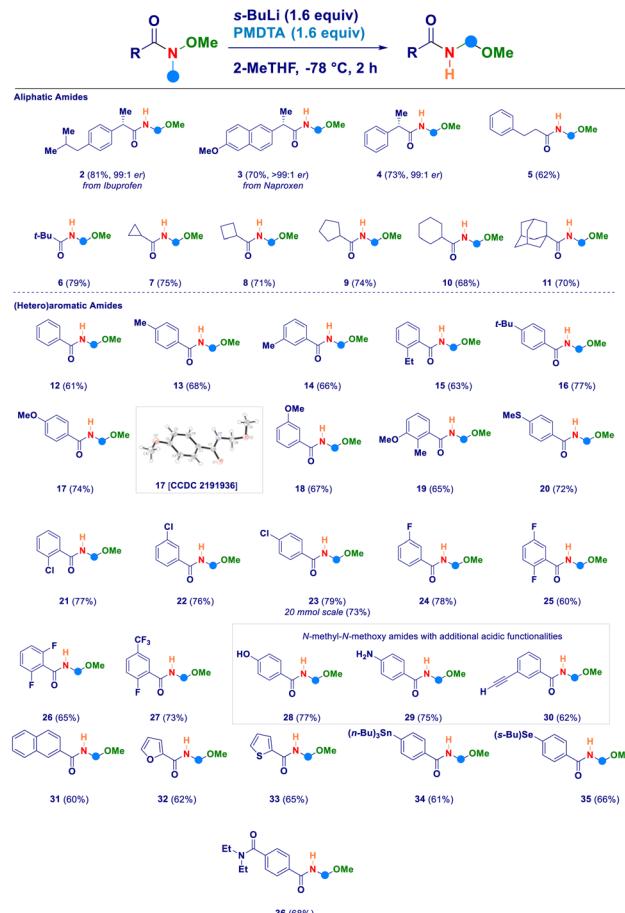


^a Unless otherwise stated, reactions were run at –78 °C for 2 h in the presence of 1.6 equiv. of the competent organolithium. ^b Isolated yields. ^c Compound **2** was obtained in 99:1 er. ^d Compound **2** was obtained in 95:5 er. ^e Reaction time 0.5 h. ^f *s*-BuLi (3.2 equiv.) was used. ^g Reaction run at –40 °C.



adduct **2a**). Pleasingly, by triggering the deaggregation (and thus the basicity)²⁹ of *s*-BuLi through the use of the bidentate ligand TMEDA (*N,N,N',N'*-tetramethylethylendiamine), the deprotonation of the N-Me group became evident, thus furnishing the desired *N*-acyl-*N,O*-acetal **2** in a promising 29% yield, though neither formation of the Graham^{20a} secondary amide **2a** nor of *s*-butyl ketone **2b** could be suppressed (entry 2). Running the reaction in diethyl ether (entry 3) or, increasing the loading of the additive resulted in no evident improvement (entry 4). The chemoselectivity slightly augmented in 2-methyltetrahydrofuran, probably, as a consequence of its higher stability under strongly basic conditions (entry 5).³⁰ Considering Bauer's observation on the complete deaggregation of *s*-BuLi in the presence of the tridentate additive PMDTA (*N,N,N',N'',N'''*-pentamethyldiethylentriamine),³¹ we were pleased in noting the almost exclusive formation of the desired adduct **2**, thus confirming the generation of the aminomethyl anion and the avoiding of Weinreb amides enolization phenomena (entry 6).^{22e} The noticeable dwindling of the yield in THF is presumably ascribed to the easier α -lithiation it undergoes – compared to 2-MeTHF – (entry 7),^{30,32} thus suggesting a strict dependence of the N-CH₃ deprotonation with the overall basicity of the reaction medium. Moreover, conducting the process in 2-MeTHF guarantees the full integrity of the stereochemical information compared to THF in which racemization phenomena became apparent (entry 6 vs. 7).³² Some additional points merit mention: (a) reactions reach completion within 2 h, as judged by lowering the reaction time to 0.5 h (entry 8); (b) keeping the stoichiometric loading of *s*-BuLi and PMDTA at 1.6 equiv. enables to maximize the formation of the desired product **2**, thus avoiding a detrimental effect on the chemoselectivity due to less controlled lithiations (entry 9); (c) replacing PMDTA with analogous polyamine ligands such as HMTETA, Me₆TREN, BDMAEE or (–)-sparteine again affected the selectivity, thus confirming the unique beneficial effect displayed by PMDTA (entries 10–14); (d) switching to alkylolithiums of distinct basicity [*i.e.* more basic *t*-BuLi (pK_a = 53) and less alkaline *n*-BuLi (pK_a = 50)]¹⁹ resulted in substantial lack of control of the transformation (entries 14–15), while the lithium amide LTMP (pK_a = 35.7)¹⁹ shifted the distribution towards the demethoxylated product **2a** (entry 16) in analogy to the previously used LDA;^{20a} (e) increasing the temperature to -40 °C lowered the reaction efficiency, as a consequence of the plausible diminished stability of the generated anion (entry 17).

Having established the four key elements governing the reaction (*s*-BuLi, PMDTA, 2-MeTHF, -78 °C), we then studied the scope of the intramolecular *N*-methyl-*N,O*-alkoxyamide homologation to *N*-acyl-*N,O*-acetals (Scheme 2). A series of Weinreb amides generated from aliphatic carboxylic acids were amenable substrates for the process: similarly to the ibuprofene analogue **2**, also the naproxene derived species smoothly underwent the transformation (**3**) with full retention of the embodied stereochemical information. This latter aspect was also deducted in the case of compound **4**, thus confirming that the employed strongly basic reaction conditions did not promote any racemization of the materials. Not only aliphatic Weinreb amides of different chemical hindrance [phenylethyl



Scheme 2 Scope of the method with *N*-methyl-*N*-methoxyamides.

(**5**) and *tert*-butyl (**6**)] on the carbonyl carbon could be used, but also a series of alicyclic analogues of progressive ring size such as cyclopropyl (**7**), cyclobutyl (**8**), cyclopentyl (**9**), cyclohexyl (**10**) and the sterically demanding adamantyl derivative (**11**). Switching to aromatic Weinreb amides did not alter the validity of the general methodology. In this context, common aliphatic substituents could be conveniently placed at different positions of the phenyl ring [*e.g.* unsubstituted (**12**), *p*-methyl (**13**), *m*-methyl (**14**), *o*-ethyl (**15**), *p*-*tert*-butyl (**16**)]. The presence of elements modulating the electrophilicity of carbonyl carbon was tolerated, as documented in the cases of: (i) electron-donating substituents such as ethers (methoxy-, **17**–**19**) or thioether (**20**) and, (ii) halogen atoms [chloro (**21**–**23**), fluoro (**24**–**26**), trifluoromethyl (**27**)]. The X-ray structural analysis of derivative **17** unambiguously confirmed the *N*-acyl-*N,O*-acetal cluster. Scaling up to 20 mmol scale did not influence the reaction yield, as shown in the case of compound **23**. Notably, the inclusion of additional acidic functionalities [OH of a phenol (**28**), NH₂ of an aniline residue (**29**) or C-H of a terminal alkyne (**30**)] were not detrimental for the homologative event whenever substrates were pretreated with MeLi (see ESI†). Moreover, polyaromatic [2-naphthyl (**31**)] and heteroaromatic [furyl (**32**) and thiienyl (**33**)] systems further expanded the reaction scope. The deprotonation *en route* to the

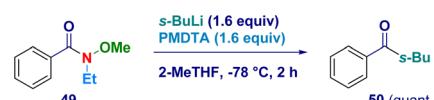


intermediate aminomethyl species did not suffer from the simultaneous presence of functionalities susceptible to lithiation, as deduced in the cases of the stannane (**34**) and the selenane (**35**). With much of our delight, the methodology enabled the selective transformation of a Weinreb amide featuring a carboxy-amide fragment (*N,N*-diethyl) into the corresponding *N*-acyl-*N,O*-acetal **36** in which no modification occurred to the functionalizing element. This is indeed an evident proof of the selective deprotonation occurring at the *N*-methyl group of the amides.

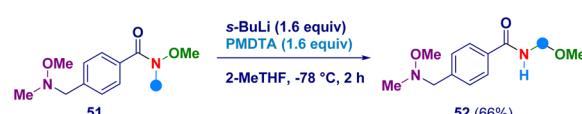
With the aim to uncover the full potential of the reaction, the evaluation of different *O*-substituted *N,O*-alkoxyamides was performed (Scheme 3). In this sense, the scope of Weinreb amides discussed above was efficiently implemented by engaging as reaction partners not only the *O*-ethyl analogues (**37**–**39**) but also the more sterically hindered *O*-*i*-propyl (**40**) and *O*-*t*-butyl (**41**) ones. The initial $\text{N}-\text{CH}_3$ deprotonation event was successfully realized also on the corresponding *O*-allyl (**42**) and the *O*-propargyl (**43**) systems, as well as, on the *O*-cyclopropylmethyl (**44**) and the *O*-methoxymethyl (**45**) analogues. The high electrophilic reactivity of the iminium species involved, enabled the smooth attack of a less nucleophilic element as the phenolate anion, thus furnishing derivative **46**. Finally, also *N*-methyl-*O*-benzyl-type alkoxyamides yielded the expected *N*-acyl-*N,O*-acetals **47** and **48** in comparable efficiency.

In order to confirm the proposed rationale, a series of control experiments were performed (Scheme 4). The pivotal presence of the *N*-methyl group as the element furnishing the active methylene unit was deduced by attempting the transformation on the *N*-ethyl-*O*-methoxy analogue **49** which simply reacted *via* canonical Weinreb mechanism giving ketone **50** as the unique product (path a). It is likely that $\text{N}-\text{CH}_2\text{CH}_3$ protons would exhibit lower acidity preventing the crucial deprotonation event with *s*-BuLi/PMDTA. Additionally, this result is also in agreement with the suitability of our conditions for preventing Graham demethoxylation.^{20a} The critical role displayed by the acyl moiety was evidenced by employing a Weinreb amide featuring a *N*-methoxy-*N*-methyl amine fragment (**51**) which yielded exclusively *N*-acyl-*N,O*-acetal **52** (path b), thus suggesting the

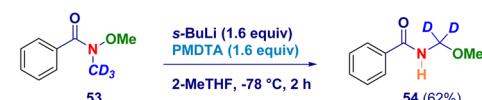
a) Requirement for *N*-methylamide



b) Selective homologation of *N*-methyl-*N*-methoxyamide



c) Use of *N*-*d*₃-methyl-*N*-methoxyamide



d) Use of *N*-methyl-*N*-*d*₃-methoxyamide

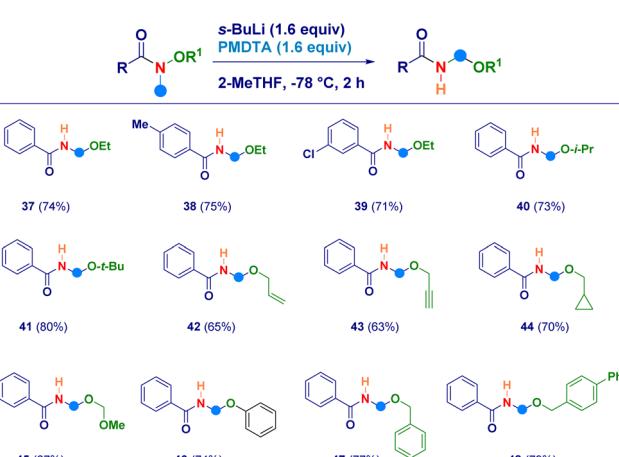


Scheme 4 Control experiments for validating the mechanistic hypothesis.

requirement for an amide functionality to promote the reaction. The unambiguous deciphering of the origin of the constitutive methylene unit of *N*-acyl-*N,O*-acetals was gathered by applying the procedure to deuterium-labeled systems. Accordingly, *N*-*d*₃-methyl-*N*-methoxy amide (**53**) was converted into the *d*₂-*N*-acyl-*N,O*-acetal **54**, thus demonstrating that the effective source for the homologated *N*-*O* linkage was the *N*-CD₃ group (path c). *Ceteris paribus*, *N*-[¹H]methyl-*N*-*d*₃-methoxy amide (**55**) was homologated to the corresponding *N*-acyl-*N,O*-[¹H]-acetal **56** featuring the labeled element exclusively at the alkoxy portion (OCD₃ – path d).

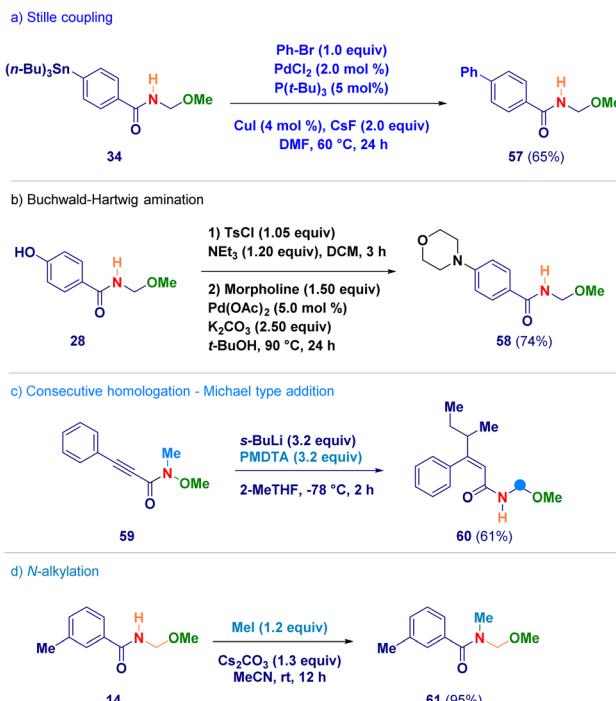
Finally, selected *N*-acyl-*N,O*-acetals were employed as starting materials for standard derivatization chemistry (Scheme 5). The stannane containing analogue **34** was used in a Stille coupling furnishing the biphenyl adduct **57** (path a);³³ upon tosylation of phenol-derivative **28**, followed by a Buchwald–Hartwig amination with morpholine, compound **58** was obtained (path b);³⁴ the alkynyl-type Michael acceptor **59** reacted – in the presence of an excess of *s*-BuLi – giving *N*-acyl-*N,O*-acetal **60** in which the excess of *s*-BuLi attacked the β -position (path c); the secondary amide functionality of adduct **14** could be efficiently alkylated under basic conditions generating **61** (path d).

In summary, we have introduced – through the homologative transformation of *N*-methyl-*N*-oxyamides to acyclic *N*-acyl-*N,O*-acetals – the concept of C1-installation within a *N*-*O* bond. The constitutive *N*-methyl moiety of the starting material acted as the source of the methylene unit. Because of the well-established reactivity of *N*-alkoxyamides in the presence of canonical homologating agents (e.g. [M]-CH₂-LG), the tactic proposed herein appears an effective tool for inserting the CH₂ group into formal oxy-amines functionalities. The controlled deprotonating event, conducted with deaggregated *s*-BuLi



Scheme 3 Synthesis of diverse *O*-substituted *N*-acyl-*N,O*-acetals.



Scheme 5 Synthetic manipulation of *N*-acyl-*N,O*-acetals.

(PMDTA), guarantees the tailored genesis of a α -aminomethyl carbanion which spontaneously rearranges to an electrophilic iminium intercepting the released alkoxide. Almost no restriction on the substitution pattern across the whole amide functionality – and, in particular on the *N*-alkoxy element – was observed, thus making flexible the access to the targeted compounds. The crucial role displayed by the *N*-methyl group was definitely ascertained through the application of the protocol to deuterium-labeled analogues.

Data availability

Further details of the experimental procedure, ¹H, ¹³C, ¹⁹F, ⁷⁷Se and ¹¹⁹Sn NMR spectra, HPLC analyses and X-ray crystallographic data for **17** are available in the ESI.†

Author contributions

M. M. and R. S. performed the experiments. W. H. realized NMR analyses and elucidated the structures. V. P. conceived and directed the project and wrote the manuscript. All the authors discussed the results.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

This work is dedicated *in memoriam* of Professor José Vicente Sinisterra Gago. We thank the University of Vienna, the

University of Turin and All4Labels Group (Hamburg, Germany) for generous funding. M. M. acknowledges the Austrian Academy of Sciences, Austrian UNESCO Commission and L'ORÉAL Austria for a L'ORÉAL FWIS Fellowship. The support from Project CH4.0 under MUR (Italian Ministry for the University) program “Dipartimenti di Eccellenza 2023-2027” (CUP: D13C22003520001) is acknowledged. Ing. A. Roller is gratefully appreciated for realizing X-ray analysis.

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