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Chemoselective synthesis of α-fluoromethyl amides *via* the controlled addition of $LiCH_2F$ to *N*-aryl and *N*-alkyl isocyanates†

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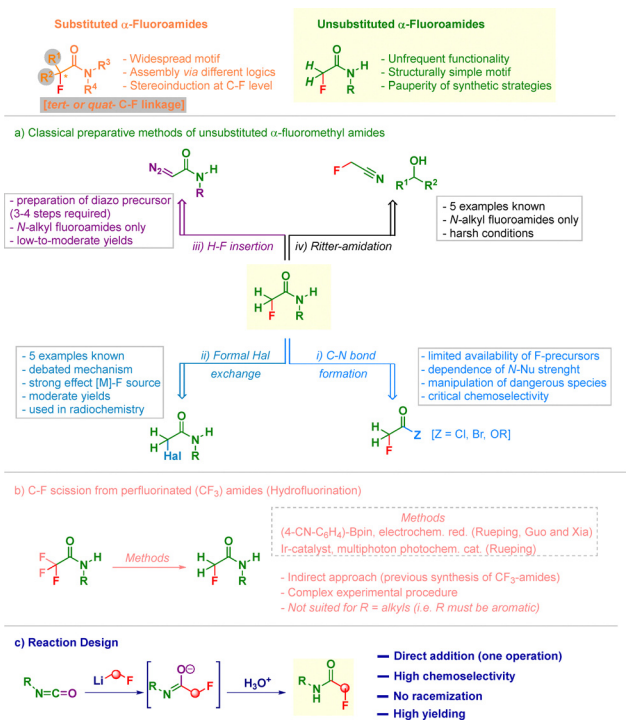
α-Fluoromethyl amides were prepared through the chemoselective nucleophilic addition of fluoromethyl-lithium to isocyanates.

Forging the amide bond represents a fundamental operation in synthesis due to its ubiquitous presence in chemistry.[1] The additional installation of a fluorine atom at the carbonyl vicinal position is a strategically convenient modulation of the chemical environment, while inducing minimal (steric) perturbation to the resulting cluster.[2] This effect arises from the unique constitutional features of the fluorine atom, including comparable radius (1.47 A *vs.* 1.21 A for hydrogen)[3] and length of C–H and C–F bonds.[4] The continuous demand from interlinked fields[5] for straightforward approaches enabling the assembly of α-monofluoroamides emerged as a remarkable endeavor due to the limited flexibility of α-functionalization techniques available for carbonyl motifs.[6] Notwithstanding, the α-fluorination of amides can be now realized through different approaches leveraging on the construction of the C–F bond through the release—to an adequate amide precursor—of the halogen in both electrophilic[7] and nucleophilic[8] regimes. Upon the judicious control of the reaction conditions a high degree of stereocontrol can be imparted to α-fluorinative carbonyl processes, as showcased by Lectka,[9] Rovis[10] and Sun.[11] The construction of α-fluoro-α-substituted amides can also be levered on rearrangement events starting from simple feedstocks. In this regard, Hu introduced a difluorocarbene precursor for merging sequential C–F and amide bond formations *via* a fluorinative-aminocarbonylation of aldehydes.[12] Also, the groups of Lan and Song[13] and Degennaro adapted the Meinwald transposition on fluorinated oxiranes for making fluoroamides.[14] Despite these advancements—conducting to secondary and tertiary C–F linkages—there is a dearth of protocols allowing the gathering of $-CH_2F$ containing amides which, despite the relative structural simplicity, have not been thoroughly studied (Scheme 1 – top).[15] The retrosynthetic analysis enables to individuate following tactics: (i) C–N bond construction starting from an amine and a monofluoromethylated carboxylic acid precursor (*e.g.* Schotten-Baumann procedure);[16] (ii) C–F bond formation



Scheme 1 General context of the presented work.

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† This work is dedicated to Professor Valeria Conte (University of Rome "Tor Vergata") in the occasion of her retirement.

via nucleophilic substitution;[17] (iii) H–F bond insertion into α-diazocarbonyls;[18] (iv) tropylium-promoted Ritter-type amidation of alcohols with fluoroacetonitrile (Scheme 1a).[19] More recently, the introduction of the hydrodefluorination tactic of perfluorinated carbon atoms (*e.g.* CF_3)—formally relying on a C–F dissociation event-,[20] are the basis for preparing α-fluoromethyl amides, as documented in the elegant electrochemical-mediated procedure developed by Rueping, Guo and Xia.[21] Indeed, hydrodefluorinations could be implemented under photocatalytic conditions, as documented by Qu and Kang[22] and the same group of Rueping (Scheme 1b).[23] Unfortunately, the aforementioned protocols are not general and are dictated by the electronic nature [alkyl or (hetero)aryl] displayed by the substituent on nitrogen. As a matter of fact, hydrodefluorination methods are restricted to *N*-aryl systems,[21–23] whereas the Ritter approach addresses uniquely the preparation of aliphatic analogues.[19] A series of additional considerations supports the demand for modular methods *en route* to the targeted α-fluoromethyl amides: (1) using C–N bond formation protocols is limited by the availability of activated fluoromethylated carboxylic derivatives and by the nucleophilicity of the employed amine; (2) the adoption of Finkelstein or hydrodefluorinative strategies are hampered by the requirement of preparing the appropriate (α-bromomethyl or α-trifluoromethyl-) precursor non commercially available; (3) this latter drawback affects also Rueping's-type hydrodefluorinations requiring the previous synthesis of trifluoromethyl-amides precursors.[21,23] Herein, is reported the rapid and chemoselective addition of CH_2F-nucleophilic element to highly electrophilic isocyanates[24] for preparing α-fluoromethyl amides (Scheme 1c). Notably, neither the nature of *N*-substituents nor the chirality in the starting materials were found detrimental for the generality of this single synthetic operation.

4-Fluorophenylisocyanate (**1**) was selected as the model substrate in the addition of $LiCH_2F$, generated *in situ* from fluoroiodomethane[25] and MeLi-LiBr (Table 1).[26]

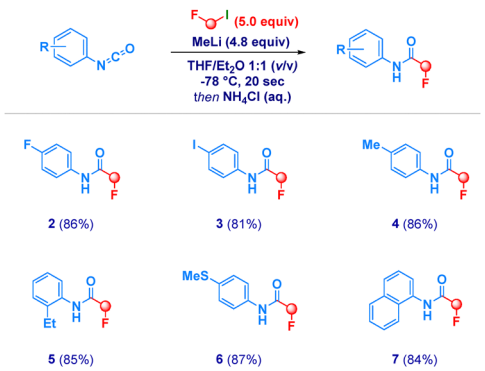
Table 1 Reaction optimization

Entry	MeLi (equiv.)	Concentrat of **1** (M)	Time (s)	Ratio[a] **2** : **2a** : **2b** : **2c**	**2** (%)[b]
1	MeLi-LiBr (2.8)	0.2	300	5 : 66 : 23 : -	Trace
2	MeLi-LiBr (2.8)	0.1	300	16 : 56 : 18 : -	10
3	MeLi-LiBr (2.8)	0.05	300	28 : 33 : 14 : 15	24
4	MeLi-LiBr (2.8)	0.05	60	39 : 31 : 12 : 7	32
5	MeLi-LiBr (2.8)	0.05	20	53 : 22 : 9 : 4	48
6	MeLi-LiBr (3.5)	0.05	20	61 : 15 : 5 : 10	55
7	MeLi-LiBr (4.0)	0.05	20	68 : 11 : 3 : 14	61
8	MeLi-LiBr (4.5)	0.05	20	71 : 7 : 3 : 17	66
9	MeLi-LiBr (5.0)	0.05	20	68 : 4 : 3 : 18	65
10[c]	MeLi (5.0)	0.05	20	91 : - : - : -	86
11	MeLi (3.5)	0.05	20	70 : 13 : 6 : -	64

$LiCH_2F$ was formed using a slight excess (0.2 equiv. compared to MeLi) of ICH_2F to ensure a quantitative I/Li exchange. [a] Determined by GC-MS analysis of the reaction crude. [b] Isolated yield. [c] ICH_2F (5.2 equiv.).

Surprisingly, symmetrical 1,2-diarylurea **2a** and 1,3,5-triarylbiuret **2b** were isolated as the major products, together with traces of the desired *N*-(4-fluorophenyl)-fluoroacetamide (**2**, entry 1). Presumably, the amide anion generated after the carbenoid attack is nucleophilic enough to attack a second equivalent of isocyanate, thus forming (sequentially) **2a** and **2b** (*vide infra* for a plausible mechanistic rationale). With the aim of suppressing these di- and tri-merization adducts,[27] we reasoned that lowering the initial concentration of the isocyanate **1** from 0.2–0.1 M (entries 1 and 2) to 0.05 M and, encouragingly **2** could be isolated in a promising 24% yield (entry 3). However, parallel to the switch of products distribution towards **2**, the fluorine/bromine exchange product **2c** was also formed. Aware of the extremely short life of the carbenoid (even at −78 °C)[26,28] and, considering that the undesired events could be promoted following the nucleophilic attack, the final acidic quenching with NH_4Cl was anticipated (entries 4–11). Thus, if realized just after 20 s from the end of the addition of MeLi-LiBr, the formation of the undesired products could be further mitigated giving **2** in good 48% yield (entry 5). Though the suppression of compounds **2a** and **2b** could be progressively achieved by employing the carbenoid in excess (3.5–5.0 equiv., entries 6–9) the presence of supra-stoichiometric LiBr (from MeLi-LiBr) boosted C–F to C–Br substitution. Under these circumstances the appearance of bromoamide **2c** could not be suppressed, as suggested by the good correlation with the loading of LiBr. Fortunately, the replacement of MeLi-LiBr with its LiBr-free analogue secured the access to fluoroamide **2** in excellent 86% yield (entry 10). The attempt of decreasing the carbenoid loading to 3.5 equiv. increases the formation of **2a** and **2b** (entry 11), thus recommending a greater excess of nucleophile. It did—however—confirm that increasing the quantity of MeLi mitigates the risk of halogens substitution (entry 11 *vs.* entry 6).

With the optimal conditions in hand, we then explored the scope of the method (Scheme 2). The protocol demonstrated flexibility and allowed the installation of the α-fluoromethyl fragment onto diverse *N*-aryl isocyanates. The genuine chemocontrol underpinning the transformation was deduced by placing an iodine atom (**3**) on the aromatic ring of the isocyanate without observing concomitant C(sp^2)–I/Li exchange. Heterocumulenes containing simple alkyl groups were amenable



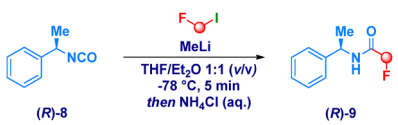
Scheme 2 Scope of the fluoromethylation of aryl-isocyanates.

starting materials (**4**-**5**), as well as thioether- (**6**) and naphthyl- (**7**) containing analogues.

Encouraged by these preliminary results and considering that only scattered examples of chiral α-fluoromethylamides are known,[16a,16b,29] we could successfully validate the protocol in the case of the enantiopure isocyanate (***R***)-**8**, thus giving the optically active α-fluoromethyl amide (***R***)-**9** in 83% yield and 99 : 1 *e.r.* (Table 2, entry 1). A series of notes are pertinent: (a) the *N*-alkyl-type substituent—slightly decreasing the electrophilicity of the isocyanate and accounting for a more pronounced steric hindrance in proximity of the (nucleophilic) nitrogen—did not induce the formation of urea and biuret byproducts even with a more favourable stoichiometry (2.8 equiv. of $LiCH_2F$), thus making not mandatory working at very low concentrations (entries 2 and 3); (b) the addition of MeLi completed within 5 min maximized the yield of (***R***)-**9** (entry 4), whereas leaving the reaction for longer time was detrimental; (c) despite the basicity of the environment, the resident chiral center remained intact without detectable racemization.

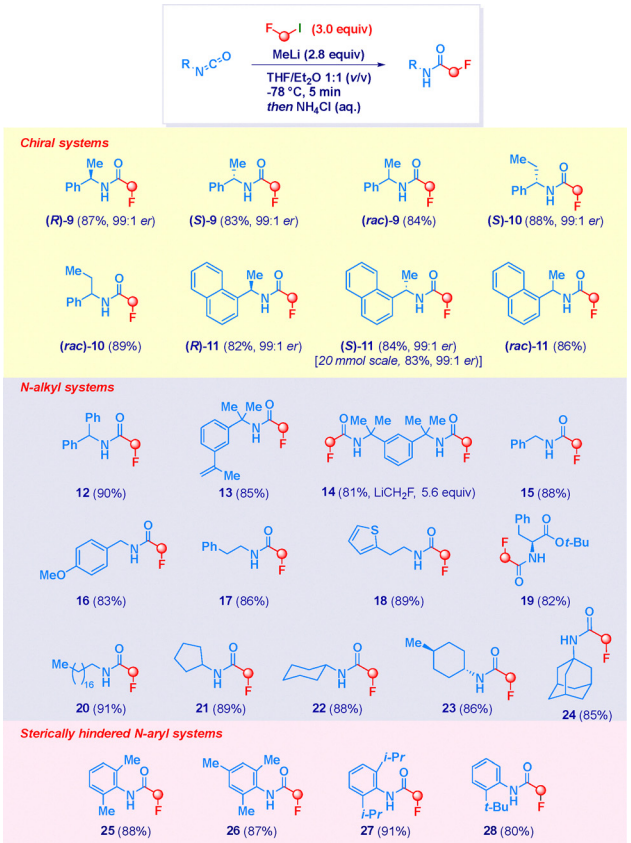
Having uncovered two sets of conditions for the fluoromethylative homologation of *N*-aryl ad *N*-alkyl-isocyanates, we next expanded the scope of the protocol (Scheme 3). The preservation of the optical purity was fully maintained during the nucleophilic addition for preparing the opposite (***S***)-**9** enantiomer, as well as, the enantiopure homologue (***S***)-**10** and both the naphthyl- analogues (***R***)-**11** and (***S***)-**11**. Scaling up to 20 mmol was possible without affecting chemical yield or optical purity. It should be noted that the present approach to chiral fluoroamides consisting of a single synthetic operation favourably compares with the only other available based on an acylative/reductive process.[16a,16b] As expected, chemical yields for racemic counterparts (***rac***)-**9**-**11** were similar. Benzhydryl isocyanate smoothly reacted to provide the corresponding derivative **12**. The increase of the steric hindrance conferred by the benzyl-type substituent on the nitrogen was not detrimental for the addition, as noted in the *tert*-systems **13** and **14**. Moreover, no cyclopropanation of the styryl substituent (**13**) was promoted by the carbenoid[30] which here manifests a true carbanion-like reactivity. The concurrent presence of two isocyanates on the substrate framework was conveniently exploited for forming the bis-(α-fluoromethyamide) **14** by simply adjusting the stoichiometry of $LiCH_2F$ (5.6 mmol).

Table 2 Reaction optimization for a chiral *N*-alkyl type isocyanate



Entry	$LiCH_2F$ (equiv.)	Concentration of **8** (M)	Time	Yield of (***R***)-**9**[a]	*e.r.* of (***R***)-**9**
1	4.8	0.05	20 s	83	99 : 1
2	2.8	0.05	20 s	61	99 : 1
3	2.8	0.10	1 min	82	99 : 1
4[b]	2.8	0.20	5 min	87	99 : 1
5	2.8	0.20	10 min	80	99 : 1

[a] Isolated yield. [b] ICH_2F (3.0 equiv.).



Scheme 3 Scope of the reaction.

Interestingly, in the series of *N*-alkyl isocyanates the gradual decreasing of the steric hindrance on the C(sp^3)–NCO group did not trigger undesirable di- and trimerization processes observable with (more electrophilic) *N*-aryl analogues when employing the nucleophile in small excess (*i.e.* 2.8 equiv.). This aspect was evident from the reactivities of isocyanates leading—among others—to benzyl-(**15**–**16**) and homobenzyl- (**17**) type derivatives. Again, acidic C–H protons on a heteroaromatic nucleus (thiophene) were untouched during the reaction, thus forming compound **18**. Of note is the fluoromethylation of the essential amino acid derivative—L-phenylalanine *tert*-butyl ester isocyanate—which occurs chemoselectively at the sp-hybridized carbon, thus making compatible the protocol for functionalizing complex systems (**19**). Furthermore, both acyclic (**20**) and cyclic (**21**–**23**) alkyl isocyanates promptly reacted to furnish the corresponding α-fluoromethyl amides in comparable chemical yields, again with stereochemical integrity (**23**). This behaviour was retained also in case of installing the high sterically demanding *N*-adamant-1-yl group (**24**). Collectively, the experimental evidence indicates that both the electronic properties and steric factors of the *N*-substituent play a critical role in determining the selectivity of the process. In this regard, it is instructive the clean and selective formation—with 2.8 equiv. of carbenoid (instead of 5.0 equiv., see Table 1) of—previously unreported—α-fluoromethyl amides **25**–**27** starting from aryl isocyanates presenting the sterically bulky 2,6-dimethyl-, 2,4,6-trimethyl- and 2,6-di-*i*-propyl-groups. Though the

latter are representatives of the class of reactive aryl-isocyanates, the embodying of sterically demanding elements in critical positions eliminates the risk of generating the aforementioned urea and biuret byproducts. As a matter of fact, the switch from 2-ethylphenyl-(**5**, Scheme 2) to 2-*tert*-butylphenyl-(**28**) substituent on the isocyanate unambiguously illustrates the effect of sterics in the control of the reaction.

The formation of urea and biuret-type byproducts can be rationalized as follows (Scheme S1 – see SI). Upon the attack of $LiCH_2F$ to the non-congested aryl isocyanate **A**, lithium imidate **B** is generated. In the productive event of α-fluoromethyl amide (**2**) formation it is quenched with acid (*path i*) However, this nucleophilic species **B** might immediately attack a second equivalent of (unreacted) isocyanate, furnishing **C** which, reiterating the sequence with a third molecule (of isocyanate), gives the biuret precursor **E** (Scheme S1 – *path ii*). Both **C** and **E** could finally undergo a CO–N cleavage triggered by the intramolecular removal of the acidic fluorine-substituted methylenic proton (see **C**′ and **E**′) which eliminating fluoroketene **D**[31] yield **2a** and **2b**. We believe that upon the removal of the acidic proton, enolate **F**′ could be obtained; afterwards, it could evolve *via* ejecting the nitrogen-centered anion (from which the urea or the biuret would be formed) and fluoroketene (Scheme S1 – *path iii*). Most probably, the weaker C(sp^2)–N bond is broken instead of the C(sp^2)–F one, as suggested by the BDE.[32] A series of evidences are diagnostic for the hypothesized scenario:[33] (a) the short-life of the carbenoid—disintegrated immediately after its generation—accounts for leaving in the reaction environment nucleophilic species like **B** and **E** which are intrinsically prone to intercept the remaining (not yet reacted) isocyanate; (b) by significantly diluting the mixture, these intermolecular processes are minimized or even precluded; (c) analogously, performing the acidic quenching just after 20 s —compatible with the generation and attack of the carbenoid—would guarantee to stop the sequence at the level of **B**, thus being productive; (d) this effect is strengthened when using an excess of carbenoid (5.0 equiv.) which maximizes the formation of **B**, thus decreasing the quantity of unreacted isocyanate; (e) the presence of sterically demanding factors on the isocyanate's nitrogen atom would impede undesired di- and tri-merizations; (f) on the other hand, the tamed electrophilicity of *N*-alkyl counterparts eliminates *per se* the risk of these undesired events. The fluoroketene elimination was confirmed by carefully quenching the reaction mixture with NaOEt (after 1 min).

In summa, we introduced a one-step protocol for the preparation of α-fluoromethyl amides *via* the addition of $LiCH_2F$ to isocyanates. The transformation exhibits good chemocontrol and chemical yields—though electron-withdrawing arylisocyanates are not competent substrates - and no racemization occurs on substrates embodying stereochemical information, thus making it primed for introducing CH_2F moieties onto sensitive molecular architectures.

Conflicts of interest

The authors declare no competing interests.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental, characterization of products, NMR and HPLC charts. See DOI: https://doi.org/10.1039/d5cc06730h.

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