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Fluorine

Access to *N*–CF_3 Formamides by Reduction of *N*–CF_3 Carbamoyl Fluorides

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Abstract: The departure into unknown chemical space is essential for the discovery of new properties and function. We herein report the first synthetic access to *N*-trifluoromethylated formamides. The method involves the reduction of bench-stable *N*CF_3 carbamoyl fluorides and is characterized by operational simplicity and mildness, tolerating a broad range of functional groups as well as stereocenters. The newly made *N*–CF_3 formamide motif proved to be highly robust and compatible with diverse chemical transformations, underscoring its potential as building block in complex functional molecules.

The exploration of unknown chemical space is considered key to reach the next frontier of innovative materials, pharmaceuticals or agrochemicals.[1] To this end, the molecular editing of crucial functional groups to currently unknown structural motifs is expected to result in novel properties and function.[2] A widely pursued modification of organic molecules is the introduction of fluorine or fluorine-containing groups, which allows to modulate the molecules' physicochemical properties such as solubility, lipophilicity, basicity, electrophilicity and metabolic stability.[3] In this context, a functionality that could so far not be edited to a *N*-trifluoromethylated analogue, is the *formamide motif* (i.e. R_2N–COH).

Aside from their uses as organocatalysts,[4] protecting groups[5] or as synthetic precursors (e.g. in heterocycle syntheses),[6] formamides are important motifs in various drugs and biologically active molecules (Figure 1, top). Representative examples are the drug Arformoterol,[7] used to fight asthma and COPD, Aplyronine A[8] as potent antitumor compound, the anti-obesity drugs Lipstatin[9] and Orlistat,[10] as well as the natural product class of antimycins. The latter represent over 40 natural products, which all share the 3-formamidosalicylate unit, and have biological functions running from antifungal to anticancer and anti-inflammatory activity.[11] Systematic studies revealed that an increased conformational flexibility of the formyl unit can be associated with higher activity.[12,13] As such, a modification of the formyl unit that lowers the *N*-lone pair availability and hence the rotational barrier could be greatly enabling. We envisioned that *N*-trifluoromethylation could potentially achieve this feat. In addition, such a modification should also increase the overall metabolic stability[14] and lipophilicity.[15] Our computational study of the antimycin core (R^1 = COMe, R^2 = Me, see Supporting Information for details) suggested that trifluoromethylation of the *N*–H would lead to an increased acidity of the phenolic OH group

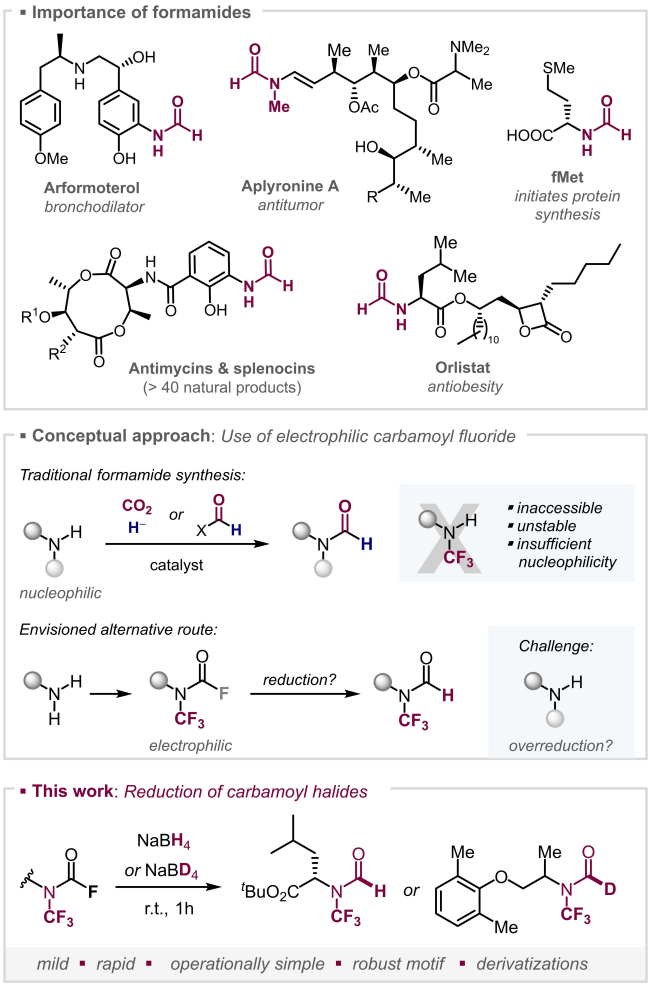

Figure 1. Importance of formamides, synthesis and challenges.

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of almost one pK_a unit (from 9.9 to 9.0) and slight reduction in barrier to rotation of >1 kcal mol^{-1} (c.f. the *N*–H congener). This increased flexibility is more pronounced when compared to the *N*–Me analogue, with barriers lowered by over 5 kcal mol^{-1},[16] and mirrors our previous experimental NMR studies with amides.[17] However, despite the growing accessibility of *N*–CF_3 compounds,[14,17,18] the corresponding *N*–CF_3 formamides are not accessible with the existing synthetic repertoire and are hence unknown.

Traditionally, methods for the synthesis of formamides use primary or secondary amines as the starting material, relying upon their inherent nucleophilicity to engage an electrophilic formyl unit.[19] However, the direct translation of this concept to *N*–CF_3 variants will not likely be a general solution to this synthetic problem due to the lack of accessibility (and stability) of secondary *N*–CF_3 amines[18i,20] as well as their attenuated nucleophilicity (Figure 1, middle).

With a goal to develop a straightforward, efficient and general method to construct *N*–CF_3 formamides, we turned our attention to *N*–CF_3 carbamoyl fluorides, which are bench-stable and easily accessible from primary amines,[17] and investigated the possibility of an F→H exchange. The substitution of fluoride by nucleophilic hydride would offer the most convenient approach. However, this process is so far unknown (also for carbamoyl halides not carrying a CF_3),[21] which might be due to challenges relating to overreduction. Indeed, the reduction of formamides to the corresponding amine with $NaBH_4$ is known.[22] This reactivity could be aggravated by the withdrawing effect of fluorine. Despite the lack of procedures to reduce carbamoyl halides in general, we nevertheless set out to study the reactivity of the corresponding *N*–CF_3 carbamoyl fluorides with hydrides.

Using a solvent mixture of DCM/MeOH (1:1) with $NaBH_4$ in our initial experiments indicated the formation of undesired *N*–CF_3 methylcarbamate along with encouraging traces of the desired *N*–CF_3 formamide. We suspected that at room temperature MeOH consumes $NaBH_4$[23] and forms alkoxyboron species which are known to perform transesterification.[24] To disfavour this undesired side-process, we turned to the sterically more demanding (and less nucleophilic) tertiary alcohol ^{t}AmOH. Pleasingly, using a mixture of DCM/^{t}AmOH (1:1), reaction of a benzylic *N*–CF_3 carbamoyl fluoride with $NaBH_4$ gave the desired *N*–CF_3 formamide **1** in 80 % yield in 1 h at room temperature as the exclusive product (see Scheme 1).

With this encouraging result in hand, we subsequently explored the wider scope (Scheme 1). Pleasingly, our method proved to be applicable to a variety of aryl and alkyl substrates. Both, electron-donating and electron-withdrawing functional groups were tolerated under these conditions, including valuable halogens (**1**, **2**, **28**, **29**), medicinally- and agrochemically-relevant trifluoromethyl and trifluoromethoxy groups (**26**, **27**), methoxy (**23**) as well as heterocycles (**11**, **32**). Pleasingly, potentially reducible functionalities, such as ester (**13**, **14**, **18**, **19**, **32**), nitrile (**31**), nitro (**33**) or alkene (**6**) remained fully untouched.

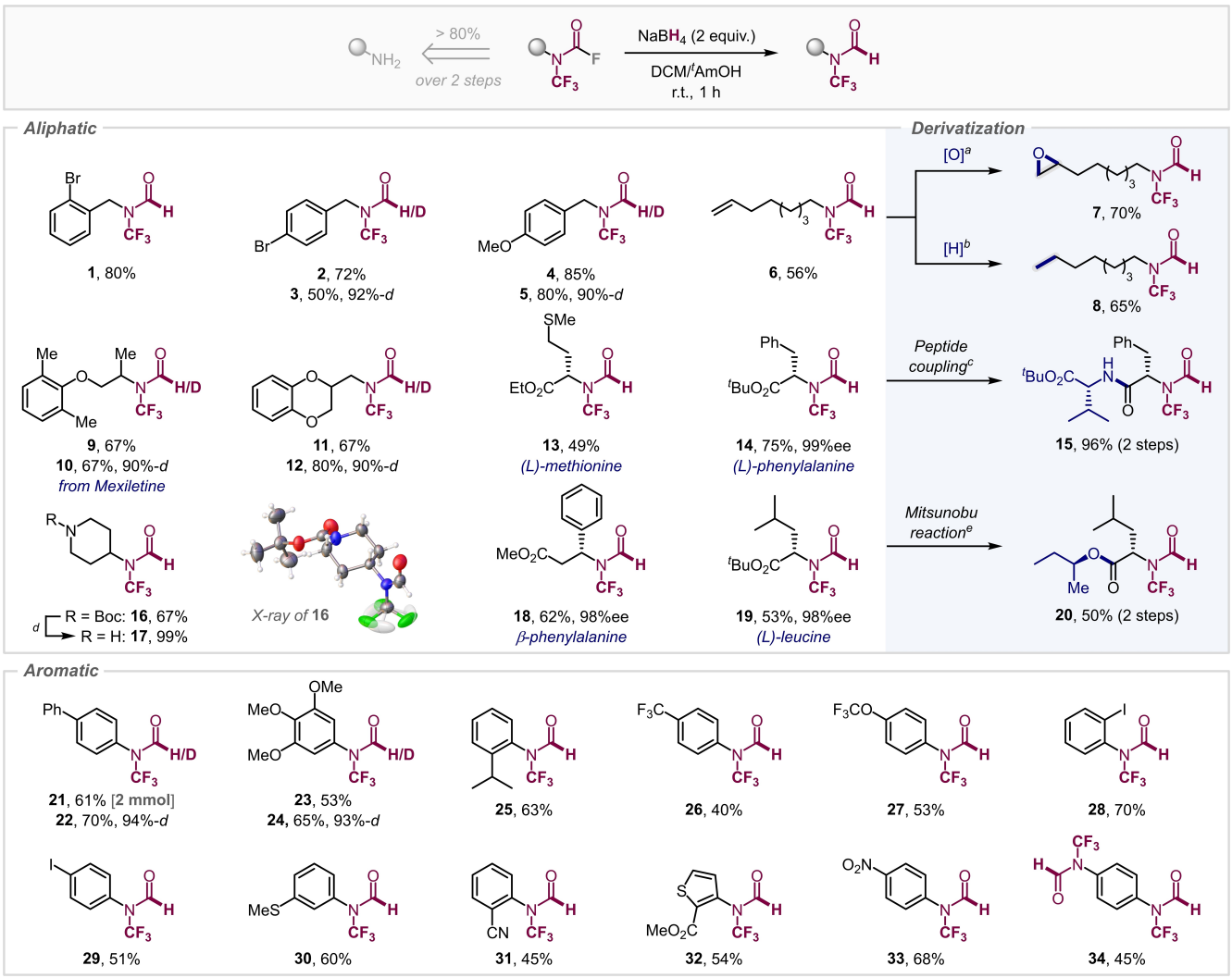
We were able to extend the exchange to synthesize deutero isotopologues via introduction of deuteride (**3**, **5**, **10**, **12**, **22**, **24**) in high efficiency, offering potentially increased metabolic stability as well as a tracer in metabolic studies.[26]

Moreover, our method unlocked access to the *N*–CF_3 formamide derivatives of both α- and β-amino acids (**14**, **18**, **19**), including the *N*–CF_3 analogue of the important fMet (**13**), which has been linked to human immune response and late-onset diseases.[27] Notably, our mild conditions allowed for full conservation of the stereochemical integrity of the employed amino acids.

With a view to exploring the chemical robustness of the newly accessed *N*–CF_3 formamides, we examined their compatibility to downstream diversification. Pleasingly, the *N*–CF_3 formamide motif proved to be highly robust, tolerating the diversification under high temperature, basic, acidic, oxidative, transition-metal-catalyzed or light-activated photo-redox conditions (see Scheme 1, right & Scheme 2, left). The pendant alkene in **6** (Scheme 1) could be oxidized (by *m*-CPBA) to epoxide **7** as well as reduced by Pd/C under an H_2 atmosphere to **8**. Additionally, deprotection of the Boc-group proceeded smoothly with **14**, followed by peptide coupling to give **15**. It is worth noting that formylated peptides are of importance in bacterial activation of nociceptors.[28] Pleasingly, the *N*–CF_3 formyl leucine underwent successful alcohol substitution under Mitsunobu conditions to give **20**, which resembles the final step of the synthesis of the anti-obesity drug *Orlistat* (and further underscores the possibility to implement the novel *N*–CF_3 motif in drug molecules).[29] Similarly, Pd-catalyzed cross-coupling methodology proved to be equally compatible: powerful Pd-catalyzed Buchwald–Hartwig amidation[30] (**35**), Sonogashira alkynylation (**36**), borylation (**37**) and carbonylation[31] (**38**) were readily performed (see Scheme 2, left). Using Pd^I dimer catalysis[32] enabled C–Br selective cross-coupling with excess organozincate to **39** without consumption of the *N*–CF_3 formamide motif. Finally, we were also able to perform an etherification with diacetone galactose to form **40** under Ni/photoredox conditions.[33] Collectively, these transformations clearly demonstrate the exquisite robustness of the novel *N*–CF_3 formamide motif as well as its potential as building block in functional molecules for medicinal, agrochemical or material sciences.[34]

Finally, we set out to examine whether our method potentially also extends to formamides that do not contain the *N*–CF_3 substituent, as there is currently no straightforward reduction of carbamoyl halides known. We were able to reduce several *N*,*N*′-disubstituted carbamoyl fluorides (**41**–**44**) and chlorides (**45**, **46**) (Scheme 2, right). Aryl and alkyl carbamoyl halides were amenable to this protocol, although extended reaction times and slightly elevated reaction temperatures were required to reach full conversion. Deuteration was also feasible, which offers an alternative approach to the synthesis of d_1-formyl compounds, circumventing the need for high pressure of CO_2 gas as commonly employed in formylations.[35]

To gain insight on the conformational flexibility, we performed variable temperature NMR studies on compounds **21** and **41** (i.e. biphenyl *N*–CF_3 formamide versus its *N*–Me analogue). These studies confirm the anticipated greater flexibility of the *N*–CF_3 formamide. While the



Scheme 1. Scope of *N*–CF_3 reduction.[25] Reaction conditions: *N*–CF_3 carbamoyl fluoride (1 equiv), $NaBH_4$ (2 equiv), DCM/^{t}AmOH (1 : 1) [0.2 M] at r.t. for 1–2 h. a) *m*-CPBA (1 equiv), DCM, 0 °C to r.t., 16 h; b) H_2 (1 atm), Pd/C (10 mol %), MeOH, r.t., 24 h; c) step 1: TFA, DCM, r.t., 16 h; step 2: HBTU, DIPEA, H-Val-O^{t}Bu·HCl, DCM, r.t., 16 h (yield over 2 steps); d) TFA (excess), $CHCl_3$, r.t., 5 h; e) step 1: TFA, DCM, r.t., 16 h; step 2: PPh_3 (1 equiv), DIAD (1 equiv), (*R*)-butan-2-ol (1 equiv), THF, r.t., 16 h (yield over 2 steps).

N–Me compound **41** showed a second rotamer up to 75 °C, consistent with literature reports,[13a] the corresponding *N*–CF_3 analogue does not even show a second rotamer at room temperature. Only upon cooling, a second rotamer becomes slightly visible from 15 °C, and clearly visible at 5 °C as judged by ^{1}H NMR and ^{19}F NMR spectroscopic analyses (see Supporting Information for additional information).

In summary, we have developed a mild and operationally simple approach to unlock the first synthetic access to *N*–CF_3 formamides via straightforward reduction of readily accessible and bench-stable *N*–CF_3 carbamoyl fluorides with $NaBH_4$ (or $NaBD_4$ to access the deutero isotopologues). The method is characterized by simplicity, rapid speed (1 h at r.t.), tolerating a wide range of functional groups, including α- and β-amino acids scaffolds under full conservation of stereochemical integrity. We showed that the method also extends more generally to carbamoyl halides not carrying the *N*–CF_3 unit, for which there is—to date—also no straightforward reduction known. The newly made *N*–CF_3 formyl motif proved to be highly robust, tolerating a wide range of synthetic manipulations under oxidative, reductive, basic or acidic conditions and including light- and/or transition metal-assisted processes. Given the prevalence of the formamide motif in therapeutic drugs as well as numerous other functional molecules, we anticipate widespread interest and application of the presented method to tailor properties and unleash new function.

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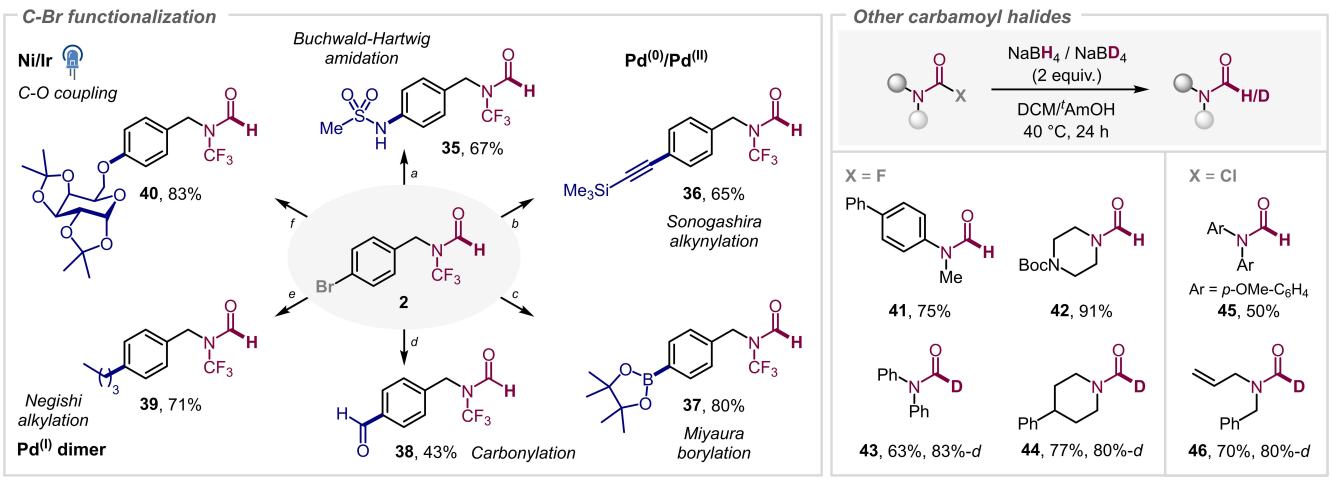

Scheme 2. Functionalization of the products (left) and extension of the method (right). a) $MeSO_2NH_2$ (1.2 equiv), $[Pd(allyl)Cl]_2$ (1 mol%), ^{t}BuXPhos (4 mol%), K_2CO_3 (2 equiv), 2-Me-THF, 80°C, 16 h; b) trimethylsilylacetylene (1.3 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), PPh_3 (10 mol%) and CuI (1.5 equiv) Et_3N (2.8 equiv), DMF, 80°C, 16 h; c) B_2pin_2 (1.1 equiv), KOAc (3 equiv), $Pd(dppf)\cdot CH_2Cl_2$ (3 mol%), DMF; d) *Chamber 1*: $Pd(dba)_2$ (10 mol%), PCy_3 (10 mol%), $KHCO_2$ (2 equiv), TBAI (0.3 equiv), butyronitrile, 100°C, 14 h. *Chamber 2*: $Pd[COD]Cl_2$ (10 mol%), P^tBu_3 (10 mol%), 9-methylfluorene-9-carbonyl chloride (COgen) (0.4 mmol), Cy_2NMe (2 equiv), butyronitrile, 100°C, 14 h; e) ^{n}BuMgCl (2 M Et_2O, 2 equiv), $ZnCl_2$ (1 M in THF, 0.22 mmol) and LiCl (2.5 M in THF, 0.22 mmol), Pd^I (2.5 mol%), r.t., 20 min; f) quinuclidine (0.1 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), $NiCl_2$·DME (5 mol%), dtbbpy (5 mol%) 1,2,3,4-di-*O*-isopropylidene-D-galactopyranose (1.5 equiv) K_2CO_3 (1 equiv), MeCN, blue LED, r.t., 24 h.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Fluorine · *N*–CF_3 Formamide · Reduction

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