LETTER

https://doi.org/10.1038/s41586-019-1518-3

Straightforward access to *N*–trifluoromethyl amides, carbamates, thiocarbamates and ureas

Thomas Scattolin[1], Samir Bouayad-Gervais[1] & Franziska Schoenebeck[1]*

Amides and related carbonyl derivatives are of central importance across the physical and life sciences[1,2]. As a key biological building block, the stability and conformation of amides affect the structures of peptides and proteins as well as their biological function. In addition, amide-bond formation is one of the most frequently used chemical transformations[3,4]. Given their ubiquity, a technology that is capable of modifying the fundamental properties of amides without compromising on stability may have considerable potential in pharmaceutical, agrochemical and materials science. In order to influence the physical properties of organic molecules—such as solubility, lipophilicity, conformation, pK_a and (metabolic) stability—fluorination approaches have been widely adopted[5–7]. Similarly, site-specific modification with isosteres and peptidomimetics[8], or in particular by *N*-methylation[9], has been used to improve the stability, physical properties, bioactivities and cellular permeabilities of compounds. However, the *N*-trifluoromethyl carbonyl motif—which combines both *N*-methylation and fluorination approaches—has not yet been explored, owing to a lack of efficient methodology to synthesize it. Here we report a straightforward method to access *N*-trifluoromethyl analogues of amides and related carbonyl compounds. The strategy relies on the operationally simple preparation of bench-stable carbamoyl fluoride building blocks, which can be readily diversified to the corresponding *N*–CF_3 amides, carbamates, thiocarbamates and ureas. This method tolerates rich functionality and stereochemistry, and we present numerous examples of highly functionalized compounds—including analogues of widely used drugs, antibiotics, hormones and polymer units.

Amide units are present in many pharmaceutical compounds[3], for example atorvastatin (Lipitor) and ledipasvir (Harvoni), which are among the best-selling drugs worldwide to date[10] (Fig. 1). Compound families that are closely related to amides—such as carbamates and ureas—are similarly influential, finding applications as insecticides, in polymers (foams, elastomers, polyurethanes), as preservatives, in cosmetics and in pharmaceuticals (for example, as chemotherapeutic and anti-HIV agents)[11–13].

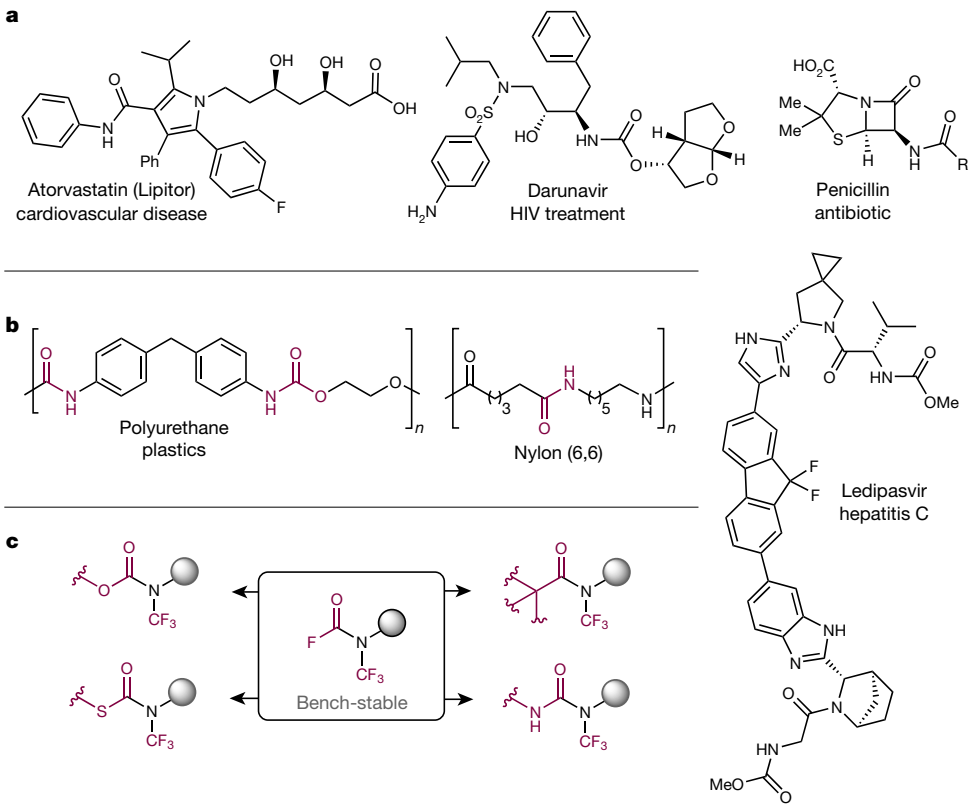

Fig. 1 | Selected examples of amides and related compounds, and this work. a, Selected pharmaceutical compounds containing an amide or a carbamate group. **b**, Representative materials containing an amide or a carbamate group. **c**, Our approach to accessing *N*–CF_3 carbonyl families from a bench-stable building block.

[1]Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany. *e-mail: franziska.schoenebeck@rwth-aachen.de

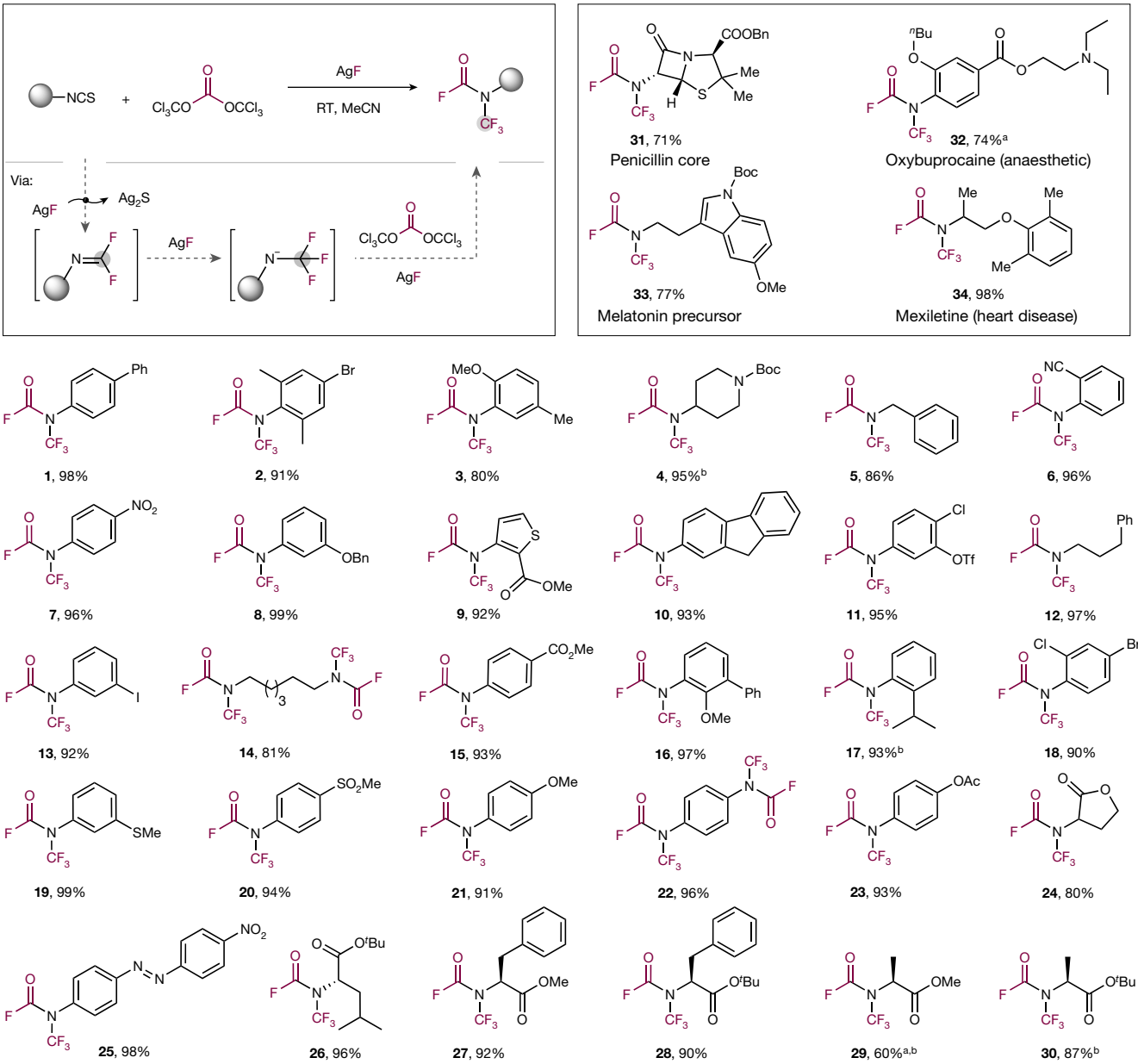

Fig. 2 | Synthesis of *N*-trifluoromethyl carbamoyl building blocks. Proposed mechanism using isothiocyanates (1.0 equiv.), BTC (0.4 equiv.) and AgF (5.0 equiv.) in acetonitrile at room temperature (RT) to generate a wide range of compounds. [a]Quantified by ^{1}H NMR analysis. [b]Reaction was carried out at 50 °C. OTf, triflate.

Despite the well established enabling effects of both *N*-methylation and fluorination, the *N*-trifluoromethylated amide motif has so far remained essentially unexplored. The most common strategy for the generation of amide bonds involves joining a primary or secondary amine with a suitable carbonyl electrophile[14]. However, this approach is unlikely to provide general access to *N*–CF_3 amides, not only because secondary trifluoromethylated amines—that is, H–N(R)(CF_3)—are difficult to synthesize[15], but also because non-aromatic examples are likely to have poor stability, resulting from the elimination of fluoride (and overall HF) assisted by the nitrogen lone pair[16]. Our group recently developed an efficient method to convert secondary amines (R_2N–H) to the corresponding tertiary trifluoromethyl amines (R_2N–CF_3)[17]. However, this methodology is applicable only for nucleophilic secondary amines, and leaves electron-deficient N–H sites in amides untouched. Considering the stability of amides, any direct chemical modification is likely to require relatively harsh reaction conditions and therefore would be of limited applicability. Indeed, the *N*-methylation of amides already presents synthetic challenges, such as the racemization of key stereocentres[2]. The indirect synthesis of the *N*–CF_3 carbonyl motif is therefore likely to be a much more promising approach.

Only a few low-functionality *N*–CF_3 amides have been prepared previously; yields were moderate, and the reactions required toxic or highly electrophilic reagents, or involved intermediates that are difficult to make[18,19]. These methods are incompatible with additional reactive functional groups or stereocentres, and also do not provide access to the wider *N*–CF_3 carbonyl families. We envisioned that a building-block approach would probably be the most enabling. As such, we focused our research on the development of a simple method to access a robust precursor, which could then potentially be modified to produce various *N*–CF_3 carbonyl compounds.

Our studies commenced with the finding that subjecting isothiocyanates to silver fluoride leads to their formal desulfurization; see Supplementary Information for mechanistic investigations. We suggest that a difluoromethyl imine[20] is generated in the process (Fig. 2), and that the use of additional silver fluoride might enable the generation of a nucleophilic derivative that could then potentially be trapped

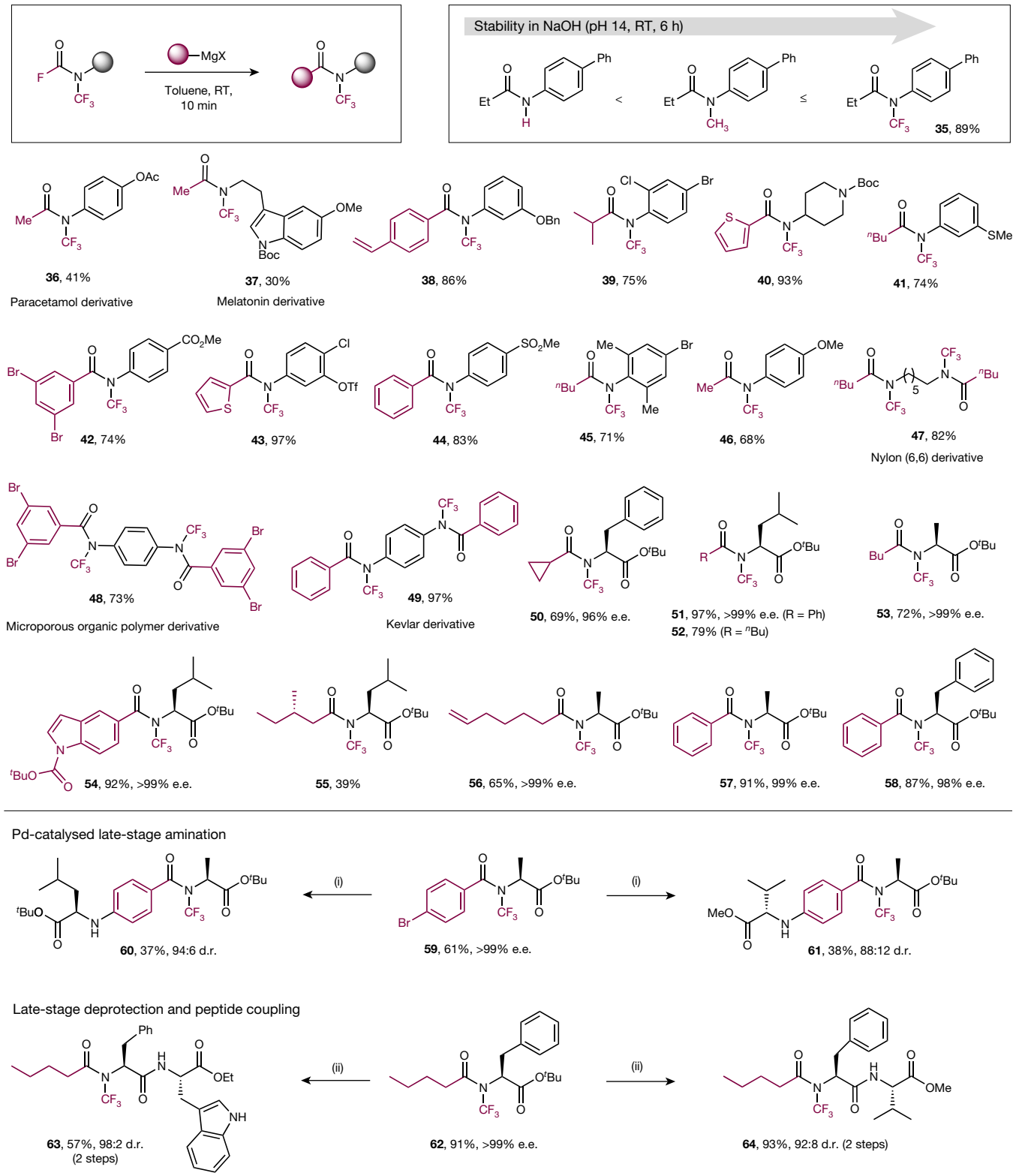

Fig. 3 | Synthesis of *N*-trifluoromethylated amides from trifluoromethyl carbamic fluorides and derivatization. Amides are accessed by reaction of R–N(CF_3)COF (1.0 equiv.) with RMgX (1.2 equiv.) in toluene at room temperature for 10 min. Reaction conditions: (i) $Pd(OAc)_2$ (10 mol%)/BINAP (15 mol%), Cs_2CO_3, toluene, 110 °C, 3 h; (ii) step 1: trifluoroacetic acid, dichloromethane, RT, 2 h; step 2: HBTU, DIPEA, amino acid, RT, 16 h. BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DIPEA, diisopropylethylamine, HBTU, 3-[bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate; d.r., diastereomeric ratio; e.e., enantiomeric excess.

by a suitable carbonyl electrophile to yield an *N*-trifluoromethylated carbonyl motif in a single step. In view of safety and practicability, we used the solid reagent bis(trichloromethyl) carbonate (BTC) as the carbonyl source, and found that we could readily convert it to the carbonyl difluoride with silver fluoride. As such, we were hopeful that a one-pot procedure—starting from readily accessible isothiocyanates (R–NCS) along with excess silver fluoride and the solid reagent BTC—might enable the direct synthesis of *N*-trifluoromethylcarbamoyl fluorides, which could then potentially serve as building blocks for further derivatization.

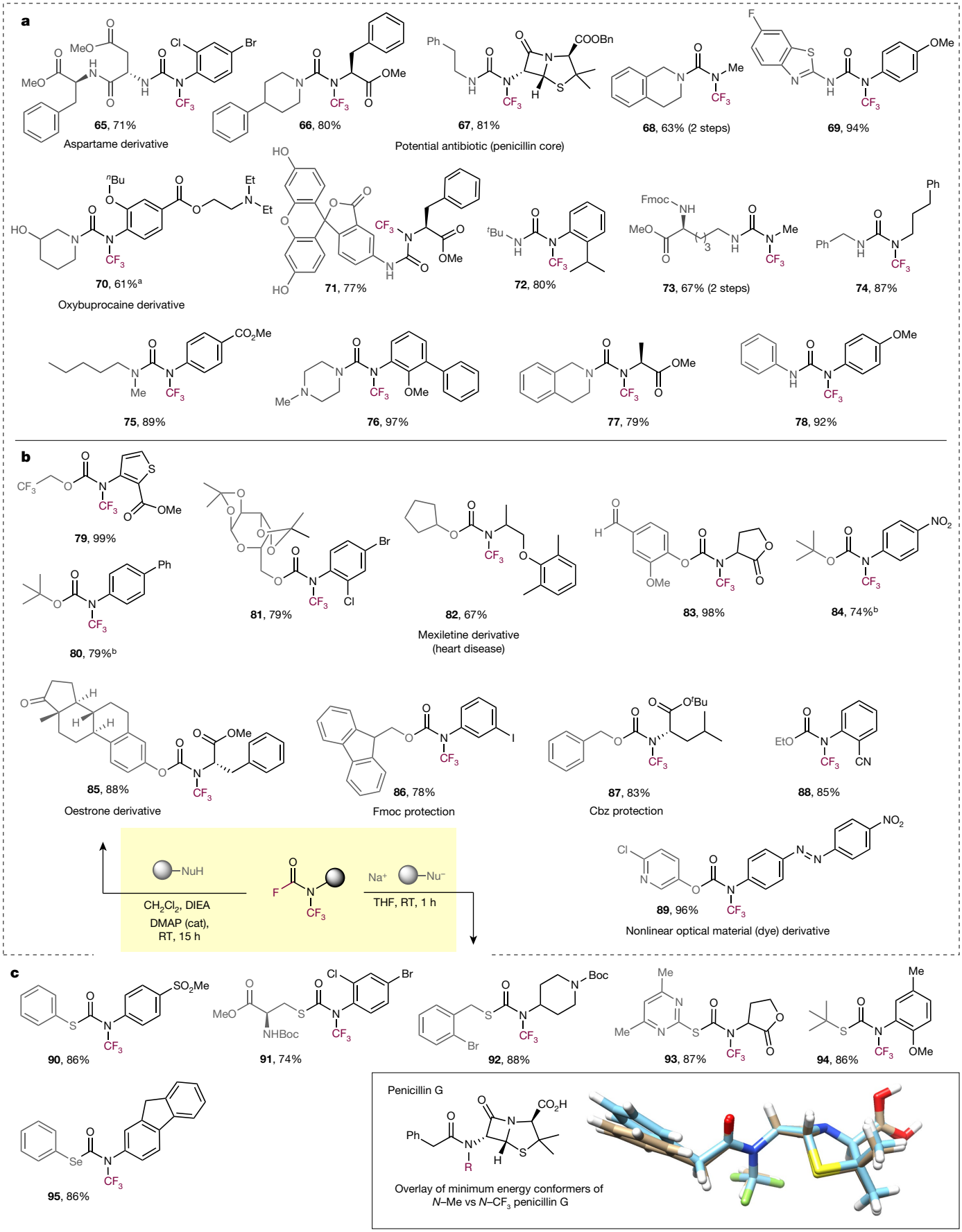

Fig. 4 | Syntheses of additional *N*–CF_3 derivatives. a, Ureas are prepared from R–N(CF_3)COF (1.0 equiv.), NuH with catalytic DMAP (0.1 equiv.) in dichloromethane at RT. **b**, Carbamates are prepared in analogy to ureas. **c**, Thio- and selenocarbamates are prepared with R–N(CF_3)COF (1.0 equiv.), NaNu (1.2 equiv.) in tetrahydrofuran (THF) at RT. [a]Quantified by ^{1}H NMR analysis. [b]Reaction was carried out with *t*BuOK as base. Calculated log *P* (where *P* is the partition coefficient) for penicillin G: 3.46 (*N*–CF_3), 2.49 (*N*–Me), 1.40 (*N*–H).

When we reacted biphenyl isothiocyanate with the solid reagent BTC and silver fluoride in acetonitrile for 16 h at room temperature, we obtained the corresponding *N*-trifluoromethylcarbamoyl fluoride **1** in 98% yield (Fig. 2). Notably, **1** proved to be stable to moisture and oxygen and could be stored on the bench. Previous synthetic routes had allowed the formation of only low-functionality analogues, in moderate yields, and using toxic reagents such as mercury salts and fluorophosgene gas[21]. Encouraged by the efficiency of the transformation, we tested whether *N*-trifluoromethylcarbamoyl fluorides of greater molecular complexity and functionality would also be accessible. The transformation proved to be very general (Fig. 2) and numerous functional groups were tolerated, such as tertiary amines (**32**), amides (**31**), nitriles (**6**), esters (**15**), sulfones (**20**), thioethers (**19**), halogens (**2**, **11**, **13** and **18**), nitro (**7**) and diazo (**25**) groups. Free alcohols, acids or primary amines required a protecting group. Optically pure protected amino acids could also be transformed with retention of stereochemistry (**26**–**30**). The substrates underwent efficient transformation at room temperature (or at slightly higher temperatures) and, after precipitation of the salt by-products with diethyl ether, the products were readily purified by filtration through Celite.

With these building blocks in hand, we next set out to develop methodology for their conversion to compounds from the broader carbonyl families. We could readily access *N*-trifluoromethyl amides from these carbamoyl fluoride precursors through the straightforward addition of a Grignard reagent at room temperature (Fig. 3). Of the solvents that we tested in this context (dichloromethane, diethyl ether, toluene and tetrahydrofuran), toluene proved to be the most effective. Alkyl, aromatic and heterocyclic substituents were efficiently introduced within 10 minutes, even in the presence of sterically demanding *ortho*-substituents (for example, **45**). The reactivity of the carbamoyl fluorides was sufficiently high as to outcompete metal–halogen exchange, enabling the syntheses of halogenated amides **39**, **43** and **45**, which could serve as valuable platforms for further derivatization (see below). We also synthesized the *N*-trifluoromethyl analogues of the hormone melatonin (**37**), the pain-relief drug paracetamol (**36**), and key structural units of macromolecules, including the bis(*N*-(trifluoromethyl)amides) **47** and **49**—the building blocks of the *N*–CF_3 analogues of nylon (6,6) and Kevlar, respectively—and **48**, which is an analogue of a microporous organic polymer precursor. Moreover, carbamoyl fluorides derived from amino acids could also be converted to the corresponding amides, provided that they were protected with a *tert*-butyl ester group. Notably, the stereochemistry was retained, resulting in amides **50**–**59** and **62** in high yields and excellent enantioselectivities (96–99% enantiomeric excess).

The wider applications of these compounds will depend both on the properties induced by the CF_3 substituent and on the overall stability of this class of compounds. Among the compounds we prepared, we observed no decomposition either of the carbamoyl fluorides or of the final target compounds. To assess the stability of the *N*–CF_3 amides, we subjected amide **35** to a solution of HCl (pH 1) or a solution of NaOH (pH 14) at room temperature for 6 h (in acetonitrile/water). We observed essentially no decomposition in acid and only a small amount of decomposition in base, whereas the corresponding *N*–Me amides showed more decomposition in base and the *N*–H analogue showed substantial decomposition in base (see Supplementary Figs. 1–11). The analogous acid and base tests on **46** and the nylon derivative **47** showed no decomposition. This suggests that the *N*-trifluoromethyl amides are rather robust and that they appear to be more stable than their *N*–H amide counterparts.

Consistent with this observed stability, we found that various follow-up synthetic transformations were also possible: the palladium-catalysed amination[22] of **59** with amino acids proceeded smoothly, and tolerated prolonged heating at 110 °C. Subjecting amide **62** to 20% trifluoroacetic acid in dichloromethane (to achieve ester cleavage), followed by peptide couplings under typical conditions, we obtained the corresponding peptides **63** and **64** in excellent yields. As such, peptides containing the *N*–CF_3 moiety can be readily prepared with this methodology, although peptides consisting solely of *N*–CF_3 analogues of naturally occurring α-amino acids are not yet accessible.

We examined the conformational properties of **35** relative to those of the *N*–Me analogue by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Although evidence of rotamers was visible in the spectrum of the *N*–Me derivative at ≤5 °C, the spectrum of the corresponding *N*–CF_3 amide (**35**) showed the presence of rotamers at temperatures lower than −45 °C; this indicates that rotation is less restricted in the *N*–CF_3 amide series. These observations are consistent with the observed infrared carbonyl stretching frequencies of these compounds and with our calculations of bond lengths, which indicate that the C–N bond is longest in the *N*–CF_3 amide. Our computational study of the *N*–CF_3 analogue of the antibiotic penicillin G (Fig. 4) indicated that the analogous conformation to that of the corresponding *N*–Me or *N*–H motifs was favoured, and predicted higher partition coefficients and pK_a values for the *N*–CF_3 analogue; see Supplementary Information.

We next explored the feasibility of synthesizing *N*–CF_3 carbonyl heteroatom motifs. The carbamoyl fluorides were not reactive towards weaker nucleophiles unless a catalytic amount of 4-dimethylaminopyridine (DMAP)[23] was added as well as base; this then enabled their transformation to the corresponding carbamates or ureas (Fig. 4). The use of stronger nucleophiles—such as alkoxides, thiolates or selenolates—resulted in efficient transformation at room temperature without the need for additives. As such, a diverse library of more than thirty examples of *N*-trifluoromethyl carbamates, -ureas, -thiocarbamates, and -selenocarbamates with rich functionality could be generated in a rapid and operationally simple manner (Fig. 4). Notable examples are the *N*–CF_3 analogues of oxybuprocaine **70** (an anaesthetic), aspartame (**65**) and the penicillin derivative **67**[24], as well as analogues of the widely used protecting groups *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and fluorenylmethyloxycarbonyl (Fmoc) (**80**, **84**, **86** and **87**), the pharmaceutical compound mexiletine **82** (used in the treatment of heart disease), the carbohydrate **81**, an analogue of the hormone oestrone (**85**), and the diazo derivative **89**, which is an analogue of the nonlinear optical material Disperse Orange 3.

Consistent with our findings for *N*–CF_3 amides, the reaction of chiral carbamoyl fluorides proceeded with retention of stereochemistry: the synthesis of carbamate **87** resulted in no detectable racemization, despite the use of DMAP and a reaction time of 15 h. Similarly, the optically pure ureas **66** and **77** were synthesized with ≤5% racemization.

In summary, we describe an operationally simple, safe, robust and general method to access the *N*-trifluoromethylcarbonyl family. The properties and stability of the *N*–CF_3 carbonyl motif set the stage for its enabling effects to be harnessed across various disciplines, ranging from fighting diseases (pharmaceuticals) and resistances (antibiotics, herbicides) to creating novel materials (polymers, coatings) and manipulating biological processes.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its supplementary information files.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests are available at https://doi.org/10.1038/s41586-019-1518-3.

Received: 18 December 2018; Accepted: 9 July 2019;
Published online 4 September 2019.

1. Greenberg, A. et al. (eds) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science* (Wiley, 2000).
2. Pattabiraman, V. R. & Bode, J. W. Rethinking amide bond synthesis. *Nature* **480**, 471–479 (2011).
3. Schneider, N., Lowe, D. M., Sayle, R. A., Tarselli, M. A. & Landrum, G. A. Big data from pharmaceutical patents: a computational analysis of medicinal chemists' bread and butter. *J. Med. Chem.* **59**, 4385–4402 (2016).

4. Brown, D. G. & Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? *J. Med. Chem.* **59**, 4443–4458 (2016).
5. Müller, K., Faeh, C. & Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **317**, 1881–1886 (2007).
6. Purser, S., Moore, P. R., Swallow, S. & Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).
7. Isanbor, C. & O'Hagan, D. Fluorine in medicinal chemistry: A review of anti-cancer agents. *J. Fluor. Chem.* **127**, 303–319 (2006).
8. Vagner, J., Qu, H. & Hruby, V. J. Peptidomimetics, a synthetic tool of drug discovery. *Curr. Opin. Chem. Biol.* **12**, 292–296 (2008).
9. Chatterjee, J., Gilon, C., Hoffman, A. & Kessler, H. *N*-methylation of peptides: a new perspective in medicinal chemistry. *Acc. Chem. Res.* **41**, 1331–1342 (2008).
10. Pharmaceutical Products and Market. *Statista* https://www.statista.com/markets/412/topic/456/pharmaceutical-products-market/.
11. Metcalf, L. R. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH, 2000).
12. Holland, J. R. et al. A controlled trial of urethane treatment in multiple myeloma. *Blood* **27**, 328–342 (1966).
13. Sijbesma, R. P. et al. Reversible polymers formed from self-complementary monomers using quadruple hydrogen bonding. *Science* **278**, 1601–1604 (1997).
14. Valeur, E. & Bradley, M. Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **38**, 606–631 (2009).
15. van der Werf, A., Hribersek, M. & Selander, N. *N*-trifluoromethylation of nitrosoarenes with sodium triflinate. *Org. Lett.* **19**, 2374–2377 (2017).
16. Klöter, G. & Seppelt, K. Trifluoromethanol (CF_3OH) and trifluoromethylamine (CF_3NH_2). *J. Am. Chem. Soc.* **101**, 347–349 (1979).
17. Scattolin, T., Deckers, K. & Schoenebeck, F. Efficient synthesis of trifluoromethyl amines through a formal umpolung strategy from the bench-stable precursor $(Me_4N)SCF_3$. *Angew. Chem. Int. Ed.* **56**, 221–224 (2017).
18. Hagooly, Y., Gatenyo, J., Hagooly, A. & Rozen, S. Toward the synthesis of the rare *N*-(trifluoromethyl)amides and the *N*-(difluoromethylene)-*N*-(trifluoromethyl)amines $[RN(CF_3)CF_2R']$ using BrF_3. *J. Org. Chem.* **74**, 8578–8582 (2009).
19. Handa, M. & Inoue, M. *O*-acyl-*N*-aryl-*N*-(trifluoromethyl)hydroxylamine derivative and method for producing the same. Japanese patent JP2012062284A (2010).
20. Ruppert, I. Organylisocyaniddifluoride R–N=CF_2 durch direktfluorierung von isocyaniden. *Tetrahedron Lett.* **21**, 4893–4896 (1980).
21. Sheppard, W. A. *N*-Fluoroalkylamines. I. Difluoroazomethines. *J. Am. Chem. Soc.* **87**, 4338–4341 (1965).
22. Pajtás, D. et al. Optimization of the synthesis of flavone–amino acid and flavone–dipeptide hybrids via Buchwald–Hartwig reaction. *J. Org. Chem.* **82**, 4578–4587 (2017).
23. Schindler, C. S., Forster, P. M. & Carreira, E. M. Facile formation of *N*-acyl-oxazolidinone derivatives using acid fluorides. *Org. Lett.* **12**, 4102–4105 (2010).
24. Clark, R. D. et al. Synthesis and evaluation of ureido- and vinylureidopenicillins as inhibitors of intraruminal lactic acid production. *J. Med. Chem.* **24**, 1250–1253 (1981).

Acknowledgements We acknowledge RWTH Aachen University for financial support, and K. Deckers and T. Sperger for assistance and discussions.

Author contributions T.S. and S.B.-G. performed the experiments. S.B.-G. undertook the calculations. All authors analysed the data and contributed to the preparation of the manuscript. F.S. wrote the manuscript.

Competing interests A patent application has been submitted by RWTH Aachen University for this methodology, with T.S. and F.S. as inventors (2018112315090400DE).

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41586-019-1518-3.

Correspondence and requests for materials should be addressed to F.S.

Peer review information *Nature* thanks Scott Bagley, Jonathan Clayden and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.