

Main-Group Catalysis

Trifluorinated Tetralins via I(I)/I(III)-Catalysed Ring Expansion:
Programming Conformation by $[\text{CH}_2\text{CH}_2] \rightarrow [\text{CF}_2\text{CHF}]$ Isosterism

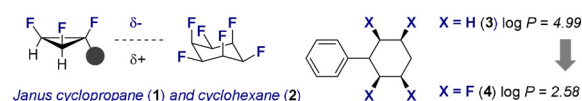
Jessica Neufeld, Timo Stünkel, Christian Mück-Lichtenfeld, Constantin G. Daniliuc, and Ryan Gilmour*

Dedicated to Professor Antonio Togni on the occasion of his retirement

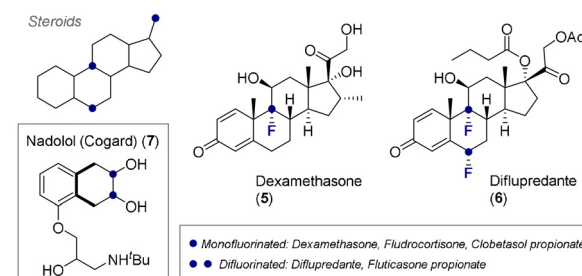
Abstract: Saturated, fluorinated carbocycles are emerging as important modules for contemporary drug discovery. To expand the current portfolio, the synthesis of novel trifluorinated tetralins has been achieved. Fluorinated methyleneindanes serve as convenient precursors and undergo efficient difluorinative ring expansion with *in situ* generated *p*-TolIF₂ (>20 examples, up to >95%). A range of diverse substituents are tolerated under standard catalysis conditions and this is interrogated by Hammett analysis. X-ray analysis indicates a preference for the CH–F bond to occupy a pseudo-axial orientation, consistent with stabilising $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$ interactions. The replacement of the symmetric $[\text{CH}_2\text{--CH}_2]$ motif by $[\text{CF}_2\text{--CHF}]$ removes the conformational degeneracy intrinsic to the parent tetralin scaffold leading to a predictable half-chair. The conformational behavior of this novel structural balance has been investigated by computational analysis and is consistent with stereoelectronic theory.

Carbocycles with tailored fluorination patterns are garnering considerable attention in the design of functional materials and therapeutics.^[1] Fluorination at multiple sites provides a molecular basis from which to modulate the physicochemical characteristics of the molecule without causing excessive alterations to the steric signature.^[2] Striking examples include the Janus ring systems developed by O'Hagan and co-workers, which range from trifluorinated cyclopropanes (1)^[3] through to the venerable all-*syn*-hexafluorocyclohexane motif (2) (Figure 1, top):^[4] This latter example is noteworthy as the fluorination pattern induces the highest calculated dipole of an organic molecule to date (6.2 D). A more recent comparison of the effects of selective tetrafluorination (3 versus 4)^[5] in significantly lowering log *P* provides compelling

Multi-fluorinated rings as drug discovery modules



Bioactive fluorinated tetrahydronaphthalene-derived structures



Trifluorinated tetralins by I(I)/I(III)-catalysed ring expansion

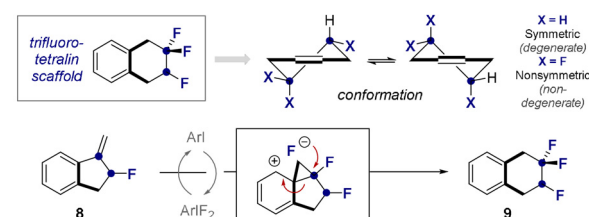


Figure 1. Top: Fluorinated carbocycles for contemporary drug discovery (1, 2 and 4). Centre: Fluorination sites in common steroids (5 and 6), and the β -blocker Nadolol (7). Bottom: An I(I)/I(III) paradigm to access the novel trifluorotetralin scaffold (8 \rightarrow 9).

evidence for the efficiency of this approach to drug discovery. These examples build upon the venerable history of monofluorination in medicinal chemistry, as is exemplified by Fried's discovery that fluorinated cortisone exhibits enhanced efficacy relative to the parent systems,^[6] and the continued success of fluorinated steroid derivatives, such as dexamethasone (5) and diflupredante (6).^[7] Intriguingly, only three sites of fluorination are commonly explored which, in turn, are dictated by preparative considerations.^[8] The two most common are positions on the B-ring of the tetralin-derived fragment. Interestingly, the dihydroxytetralin motif constitutes the core of the β -blocker Nadolol (Cogard®) (7), further underscoring the importance of electronegative substituents at the saturated periphery of the tetrahydronaphthalene core (Figure 1, centre). Motivated by the pallet of opportunities that multiply fluorinated carbocycles offer, the success of H/OH \rightarrow F bioisosterism,^[1,2] and the prevalence of tetralin-derivatives in nature,^[9,10] a route to generate fluorinated tetralin motifs would expand the portfolio of novel motifs for

[*] M. Sc. J. Neufeld, B. Sc. T. Stünkel, Dr. C. Mück-Lichtenfeld, Dr. C. G. Daniliuc, Prof. Dr. R. Gilmour
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 36, 48149 Münster (Germany)
E-mail: ryan.gilmour@uni-muenster.de
Homepage: <https://www.uni-muenster.de/Chemie.oc/gilmour>

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.202102222>.

© 2021 The Authors. Angewandte Chemie International Edition published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

molecular design.^[11] Specifically, the trifluoro motif resulting from isosteric replacement of the symmetric [CH₂-CH₂] motif distal to the aryl ring by [CF₂-CHF] would circumvent the conformational lability intrinsic to the parent tetralin scaffold: the introduction of hyperconjugative interactions ($\sigma_{C-H} \rightarrow \sigma_{C-F}^*$) would render the two half chairs non-degenerate. To access this novel class of fluorinated heterocycles, fluorinated methyleneindanes (**8**) were selected as substrates. It was envisaged that exposure to in situ generated *p*-TolIF₂^[12] under the auspices of I(I)/I(III) catalysis^[13,14,15] would induce a fluorinative ring expansion via an ephemeral, tricyclic phenonium ion^[16] to liberate the desired product (**9**) (Figure 1, bottom).

Confidence in the feasibility of this catalysis-based strategy stemmed from a plenum of stoichiometric ring expansion processes. Pertinent examples include the generation of difluoro ethers from aryl-substituted ketones using XeF₂ by Zupan and co-workers.^[17] Furthermore, the ability of hypervalent iodine reagents to induce ring expansion with Pd and Cu or BF₃·OEt₂, has been elegantly demonstrated by the groups of Szabo^[14e] and Murphy,^[14g,j] respectively. To devise a catalysis-based platform to access novel, trifluorinated tetralins, 2-fluoro-methyleneindane (**8**) was selected as a model substrate for reaction optimisation (Table 1). It was envisaged that this allyl fluoride would engage with *p*-TolIF₂, generated by in situ oxidation from inexpensive *p*-TolI, to forge the desired carbocycle **9**, where the CHF unit would function as a conformational control unit.

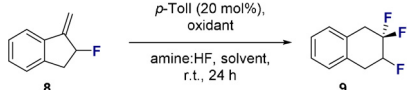
Initially, the transformation was investigated using Selectfluor as the terminal oxidant in CHCl₃ at ambient temperature using HF as a convenient fluoride source. Given the

importance of Brønsted acidity in ArIX₂ mediated processes,^[15d,18] variation of the amine:HF ratio was explored using mixtures of commercially available NEt₃:HF 1:3 and pyr:HF 1:9.2 (Olah's reagent). Initial attempts to induce difluorinative ring expansion with an amine:HF ratio of 1:3 generated the desired *geminal* fluorinated tetralin **9** in only 7% yield (Table 1, entry 1). However, adjusting the ratio to 1:4.5 led to a significant enhancement in efficiency (61%, entry 2). Further increasing the amine:HF ratio to 1:6 proved to be detrimental (47%, entry 3) and thus the remainder of the study was conducted with amine:HF 1:4.5. A solvent screen (entries 4–9) identified DCE as being the optimal reaction medium for the title transformation (74% yield, entry 5). Fluorinated solvents such as hexafluoroisopropanol (HFIP) and ethyl trifluoroacetate (ETFA) led to moderate yields (48% and 56%, respectively, entries 6–7). Furthermore, non-halogenated solvents proved to be detrimental (entries 8–9). Replacing Selectfluor with *m*-CPBA (entry 10) or oxone (entry 11) did not lead to an improvement, nor did increasing or decreasing temperature (entries 12 and 13). Lowering the catalyst loading led to a slight decrease in yield, and the control experiment without *p*-TolI supports the involvement of an I(I)/I(III) catalysis paradigm (54% and < 5%, respectively, entries 14–15).

Having established suitable reaction conditions for the difluorinative ring expansion (Table 1, entry 5) the scope and the limitations of the transformation were explored (Scheme 1). Initially, the parent scaffold **9** was prepared under the standard reaction conditions, and the process could be scaled up to 1 mmol without loss of catalytic efficiency. Halogens were found to be compatible with this protocol as is exemplified by products **10–14** (up to > 95% yield), enabling the regioisomeric bromides **12–14** to be prepared as synthetically-versatile coupling partners for downstream manipulation. Although it was possible to generate the methyl-derivative **15**, the disparity in yield when compared with electron deficient systems prompted a more detailed Hammett analysis (vide infra). Electron-deficient substrates proved to be highly competent precursors as exemplified by the triflate (**16**), trifluoromethyl (**17**) and cyano (**18**) species (up to 92% yield). Phthalimide **19** was smoothly generated to provide access to masked aniline derivatives, and a substrate with a pendant α,β -unsaturated ester (**20**) demonstrates the chemoselectivity of the transformation. The addition of substituents on the saturated ring system was tolerated (**21** and **22**), and catalysis enabled the formation of the tetrafluorinated compound **23** and mixed halogen system **24**. In all cases, reactions performed in the absence of *p*-TolI led to < 5% yield for **9–24**. To correlate the electronic signature of the aryl fragment with catalysis efficiency, the Hammett values σ_p and σ_m of several electronically diverse compounds were plotted against the ¹⁹F NMR yields (Scheme 1, bottom). The plot underscores the fact that strong electron-withdrawing groups on the aryl fragment facilitate difluorinative ring expansion.

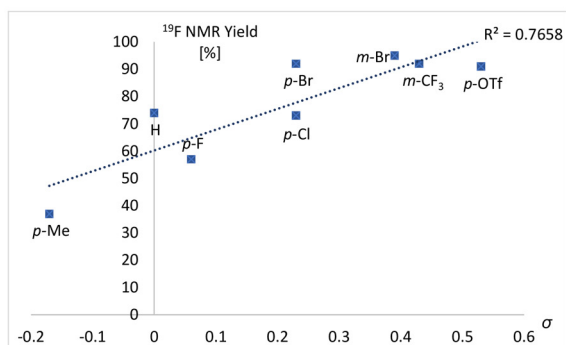
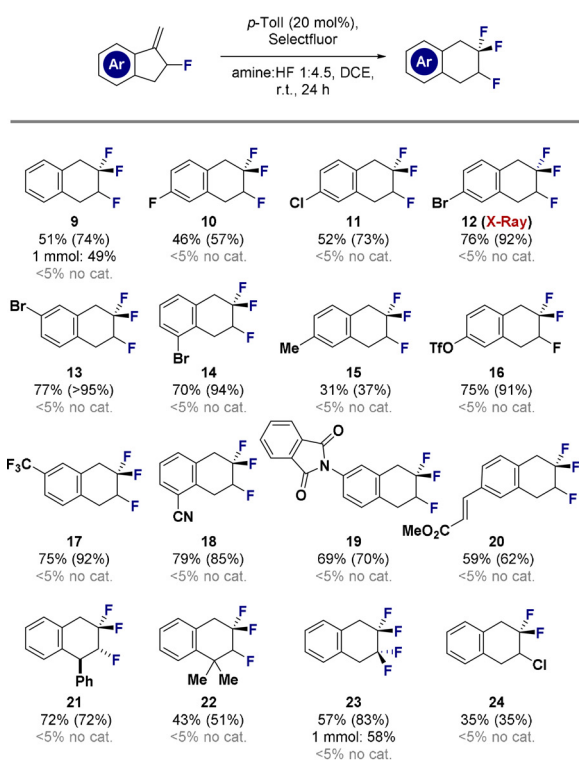
To confirm that electron-rich groups suppress catalysis (see Scheme 1, lower), the difluorinative ring expansion to generate **25** was attempted, but led to degradation of the starting material (Scheme 2). Furthermore, the requirement

Table 1: Optimisation of the reaction conditions.



entry ^[a]	oxidant	amine:HF ^[b]	solvent	yield ^[c]
1	Selectfluor	1:3.0	CHCl ₃	7%
2	Selectfluor	1:4.5	CHCl ₃	61%
3	Selectfluor	1:6.0	CHCl ₃	47%
4	Selectfluor	1:4.5	CH ₂ Cl ₂	71%
5	Selectfluor	1:4.5	DCE	74%
6	Selectfluor	1:4.5	HFIP	48%
7	Selectfluor	1:4.5	ETFA	56%
8	Selectfluor	1:4.5	toluene	54%
9	Selectfluor	1:4.5	CH ₃ CN	28%
10	<i>m</i> -CPBA	1:4.5	DCE	63%
11	Oxone	1:4.5	DCE	39%
12 ^[d]	Selectfluor	1:4.5	DCE	65%
13 ^[e]	Selectfluor	1:4.5	DCE	29%
14 ^[f]	Selectfluor	1:4.5	DCE	54%
15 ^[g]	Selectfluor	1:4.5	DCE	< 5%

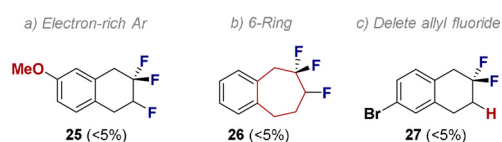
[a] Standard reaction conditions: **8** (0.2 mmol), *p*-TolI (20 mol%), oxidant (1.5 equiv.), solvent (0.5 mL), amine:HF (0.5 mL), ambient temperature, 24 h. [b] See supporting information for the exact calculation of the amine:HF mixtures. [c] Determined by ¹⁹F NMR analysis of the crude reaction mixture using ethyl fluoroacetate as internal standard. [d] Reaction was performed at 50°C. [e] Reaction was performed at 0°C. [f] Reaction was performed with 10 mol% catalyst. [g] Reaction was performed without catalyst.



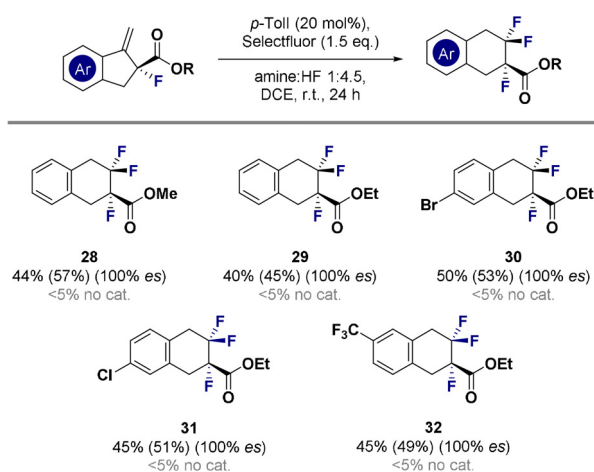
Scheme 1. Top: Exploring the scope of the reaction. Standard reaction conditions: substrate (0.2 mmol), *p*-Toll (20 mol%), Selectfluor (1.5 equiv.), DCE (0.5 mL), amine:HF 1:4.5 (0.5 mL), ambient temperature, 24 h. Yields refer to isolated products while ¹⁹F NMR yields are given in parentheses (determined by ¹⁹F NMR analysis of the crude reaction mixture using ethyl fluoroacetate as internal standard). Bottom: Effect of arene electron density on reaction efficiency. N.B. **Care must be taken during isolation due to the volatility of the products.**

for fluorinated methyleneindanes is demonstrated through the failed attempts to generate **26** and **27**. The latter example, in which the allyl fluoride is essential, distinguishes this catalysis-based platform from stoichiometric examples using the non-fluorinated methyleneindane.^[14j,19]

Given the plenum of methods to enable the enantioselective fluorination of β-ketoesters,^[20] which can be processes to optically active precursors, it was envisaged that ring expansion would provide a route to access enantio-enriched trifluorinated products (Scheme 3). Despite the addition of an additional electron-withdrawing group, catalysis was observed under the standard conditions reported (**28–32**, up to 57% yield). The ester and C(sp²)-Br motifs in compound



Scheme 2. Control reactions. Standard reaction conditions: substrate (0.2 mmol), *p*-Toll (20 mol%), Selectfluor (1.5 equiv.), DCE (0.5 mL), amine:HF 1:4.5 (0.5 mL), ambient temperature, 24 h. Yields refer to ¹⁹F NMR yields (determined by ¹⁹F NMR analysis of the crude reaction mixture using ethyl fluoroacetate as internal standard).



Scheme 3. Exploring the scope of the reaction. Standard reaction conditions: substrate (0.2 mmol), *p*-Toll (20 mol%), Selectfluor (1.5 equiv.), DCE (0.5 mL), amine:HF 1:4.5 (0.5 mL), ambient temperature, 24 h. Yields refer to isolated products while ¹⁹F NMR yields are given in parentheses (determined by ¹⁹F NMR analysis of the crude reaction mixture using ethyl fluoroacetate as internal standard). N.B. **Care must be taken during isolation due to the volatility of the products.**

30 render it a convenient linchpin for bidirectional functionalisation. Moreover, the optical purity of the products was not compromised under the standard catalysis conditions (100% es).

To explore the conformational consequences of replacing the symmetric [CH₂-CH₂] motif by an isosteric non-symmetric [CF₂-CHF] group in tetralins [*V*_{vdw} 138 Å³ versus 156 Å³ for tetralin and **9**, respectively],^[21] X-ray analysis of a representative example was conducted. It was envisaged that isosteric replacement of [CH₂-CH₂] by [CF₂-CHF] would bias the conformation, thereby bypassing the degeneracy of the two half chairs in the parent system (Figure 2). In the case of compound **12**, the conformer in which the C(sp³)-F of the CHF unit adopts a *quasi*-axial orientation is observed.^[22] This allows for stabilising hyperconjugative [σ_{C-H}→σ_{C-F}*] interactions, as is evident from the difference in C-F_{ax} and C-F_{eq} bond lengths (1.442 and 1.428 versus 1.326 Å, respectively, Δ*d*_{C-F(ax-eq)} 0.1 Å).

To quantify this interaction, a conformational analysis of compound **12** was conducted at the DFT level of theory (Please see the Supporting Information for full details). The optimised molecular structures (TPSS-D3/def2-TZVP) of the two half chair conformers **12-a** and **12-b** (Figure 3), confirm

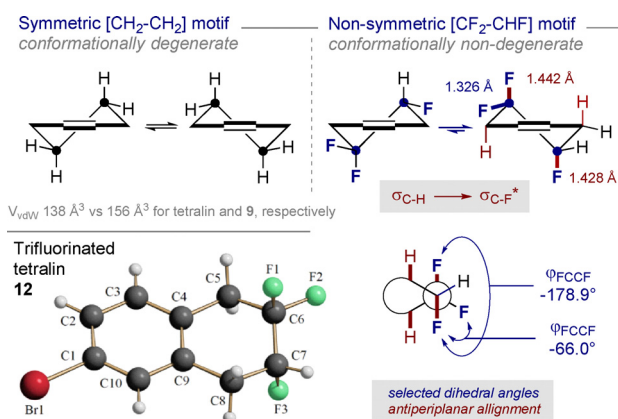


Figure 2. X-ray crystal structure of tetralin 12.^[22]

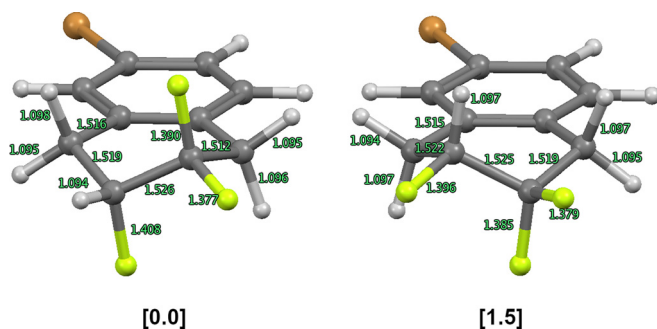


Figure 3. Optimised molecular structure (TPSS-D3/def2-TZVP) of 12-a (left) and alternative conformer 12-b (right). Internuclear distances are given in Å. In square brackets: relative free energies ΔG_{298} (PW6B95-D3//TPSS-D3/def2-TZVP) in kcal mol⁻¹.

a preference for the pseudo-axial species ($\Delta\Delta G_{298} + 1.0$ kcal mol⁻¹), and the calculated bond lengths are in good agreement with the experimental values. A NBO second order perturbation analysis reveals that the largest contribution arises from vicinal $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$ interactions, which is fully in line with the working hypothesis.

In conclusion, a main group catalysis-based strategy has been leveraged to access novel trifluorinated tetralins by difluorinative ring expansion of fluorinated methyleneindanes. Isosteric replacement of the symmetric $[\text{CH}_2\text{-CH}_2]$ motif by a non-symmetric $[\text{CF}_2\text{-CHF}]$ group [$\Delta V_{\text{vdW}} = \text{ca. } 13\%$] at the distal edge of the saturated carbocycle removes the conformational degeneracy inherent to the parent system. The stabilising hyperconjugative interactions [$\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$] that underpin this effect manifest themselves in the X-ray crystal structure analysis ($\Delta d_{\text{C-F(ax-eq)}} 0.1 \text{ \AA}$) and have been interrogated by DFT analysis. It is envisaged that these novel tetralins, and the stereoelectronic bias that governs pre-organisation, will find application in focused medicinal chemistry and molecular design in a broader sense.

Acknowledgements

The WWU Münster and the Deutsche Forschungsgemeinschaft (SFB 858, fellowship to J.N.) are acknowledged for

generous financial support. We thank Dr. Klaus Bergander (WWU) for support with NMR analysis. Open access funding enabled and organized by Projekt DEAL.

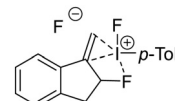
Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorination · iodine(III) · organocatalysis · ring expansion · tetralin

- [1] a) D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7981–7997; b) Y.-H. Lam, C. Bobbio, I. R. Cooper, V. Gouverneur, *Angew. Chem. Int. Ed.* **2007**, *46*, 5106–5110; *Angew. Chem.* **2007**, *119*, 5198–5202; c) R. Mondal, M. Agbaria, Z. Nairoukh, *Chem. Eur. J.* **2021** <https://doi.org/10.1002/chem.202005425>.
- [2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; d) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871; *Angew. Chem.* **2011**, *123*, 12062–12074; e) D. O'Hagan, H. Deng, *Chem. Rev.* **2015**, *115*, 634–649; f) M. El. Qacemi, S. Rendine, P. Mainfisch, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier Inc, Amsterdam, **2019**, pp. 607–623.
- [3] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.
- [4] a) N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, *Nat. Chem.* **2015**, *7*, 483–488; b) N. Santschi, R. Gilmour, *Nat. Chem.* **2015**, *7*, 467–468; c) B. E. Ziegler, M. Lecours, R. A. Marta, J. Featherstone, E. Fillion, W. S. Hopkins, V. Steinmetz, N. S. Keddie, D. O'Hagan, T. B. McMahon, *J. Am. Chem. Soc.* **2016**, *138*, 7460–7463; d) For a synthetic study, see M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908–912.
- [5] A. Rodil, S. Bosisio, M. S. Ayoub, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.
- [6] For the discovery that fluorinated cortisone is more potent than the non-fluorinated systems, see: J. Fried, A. Borman, W. B. Kessler, P. Grabowich, E. F. Sabo, *J. Am. Chem. Soc.* **1958**, *80*, 2338–2339.
- [7] For a report demonstrating that F-vitamin D₃ is more potent than the non-fluorinated analogue, see: J. L. Napoli, M. A. Fivizzani, H. K. Schnoes, H. F. DeLuca, *Biochemistry* **1979**, *18*, 1641–1646.
- [8] I. Herraiz, *Methods in Molecular Biology* **2017**, https://doi.org/10.1007/978-1-4939-7183-1_2.
- [9] a) B. Holmbom, C. Eckerman, P. Eklund, J. Hemming, L. Nisula, M. Reunanen, R. Sjöholm, A. Sundberg, K. Sundberg, S. Willför, *Phytochem. Rev.* **2003**, *2*, 331–340; b) W. K. Brewster, D. E. Nichols, R. M. Riggs, D. M. Mottola, T. W. Lovenberg, M. H. Lewis, R. B. Mailman, *J. Med. Chem.* **1990**, *33*, 1756–1764; c) M. Kvasnica, L. Rarova, J. Oklestkova, M. Budesinsky, L. Kohout, *Bioorg. Med. Chem.* **2012**, *20*, 6969–6978; d) M. J. Hatfield, L. G. Tsurkan, J. L. Hyatt, C. C. Edwards, A. Lemoff, C. Jeffries, B. Yan, P. M. Potter, *J. Nat. Prod.* **2013**, *76*, 36–44.
- [10] For selected studies on tetrahydronaphthalenes, see: a) T.-X. Liu, F.-B. Li, G.-W. Wang, *Org. Lett.* **2011**, *13*, 6130–6133; b) D. Naduthambi, S. Bhor, M. B. Elbaum, N. J. Zondlo, *Org. Lett.* **2013**, *15*, 4892–4895; c) S.-I. Nakano, K. Kakugawa, T. Nemoto, Y. Hamada, *Adv. Synth. Catal.* **2014**, *356*, 2088–2096; d) N. Ishida, N. Ishikawa, S. Sawano, Y. Masuda, M. Murakami, *Chem.*

- Commun.* **2015**, *51*, 1882–1885; e) J. C. T. Reddel, W. Wang, K. Koukounas, R. J. Thomson, *Chem. Sci.* **2017**, *8*, 2156–2160; f) L. Wang, F. Wu, J. Chen, D. A. Nicewicz, Y. Huang, *Angew. Chem. Int. Ed.* **2017**, *56*, 6896–6900; *Angew. Chem.* **2017**, *129*, 7000–7004.
- [11] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359; c) I. G. Molnár, C. Thiehoff, M. C. Holland, R. Gilmour, *ACS Catal.* **2016**, *6*, 7167–7173.
- [12] a) C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961–3964; b) S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, *Chem. Sci.* **2014**, *5*, 2754–2760; c) J. C. Sarie, C. Thiehoff, R. J. Mudd, C. G. Daniliuc, G. Kehr, R. Gilmour, *J. Org. Chem.* **2017**, *82*, 11792–11798; d) J. Häfliger, C. R. Pitts, D. Bornemann, R. Käser, N. Santschi, J. Charpentier, E. Otth, N. Trapp, N. Verel, H. P. Lüthi, A. Togni, *Chem. Sci.* **2019**, *10*, 7251.
- [13] For selected reviews, see a) N. Yoneda, *J. Fluorine Chem.* **2004**, *125*, 7–17; b) S. V. Kohlhepp, T. Gulder, *Chem. Soc. Rev.* **2016**, *45*, 6270–6288; c) A. M. Arnold, A. Ulmer, T. Gulder, *Chem. Eur. J.* **2016**, *22*, 8728–8739; d) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.
- [14] For selected examples of 1,1-difluorination, see: a) S. Hara, J. Nakahigashi, K. Ishi-I, T. Fukuhura, N. Yoneda, *Tetrahedron Lett.* **1998**, *39*, 2589–2592; b) N. O. Ilchenko, B. O. A. Tasch, K. J. Szabó, *Angew. Chem. Int. Ed.* **2014**, *53*, 12897–12901; *Angew. Chem.* **2014**, *126*, 13111–13115; c) T. Kitamura, K. Muta, J. Oyamada, *J. Org. Chem.* **2015**, *80*, 10431–10436; d) S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51–54; e) N. O. Ilchenko, K. J. Szabó, *J. Fluorine Chem.* **2017**, *203*, 104–109; f) F. Scheidt, J. Neufeld, M. Schäfer, C. Thiehoff, R. Gilmour, *Org. Lett.* **2018**, *20*, 8073–8076; g) Z. Zhao, L. Racicot, G. K. Murphy, *Angew. Chem. Int. Ed.* **2017**, *56*, 11620–11623; *Angew. Chem.* **2017**, *129*, 11778–11781; h) T. Kitamura, K. Yoshida, S. Mizuno, A. Miyake, J. Oyamada, *J. Org. Chem.* **2018**, *83*, 14853–14860; i) W.-X. Lv, Q. Li, J.-L. Li, Z. Li, E. Lin, D.-H. Tan, Y.-H. Cai, W.-X. Fan, H. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 16544–16548; *Angew. Chem.* **2018**, *130*, 16782–16786; j) Z. Zhao, A. J. To, G. K. Murphy, *Chem. Commun.* **2019**, *55*, 14821–14824.
- [15] For selected examples of 1,2-difluorination, see a) S. M. Banik, J. W. Medley, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003; b) I. G. Molnár, R. Gilmour, *J. Am. Chem. Soc.* **2016**, *138*, 5004–5007; c) M. K. Haj, S. M. Banik, E. N. Jacobsen, *Org. Lett.* **2019**, *21*, 4919–4923; d) F. Scheidt, M. Schäfer, J. C. Sarie, C. G. Daniliuc, J. J. Molloy, R. Gilmour, *Angew. Chem. Int. Ed.* **2018**, *57*, 16431–16435; *Angew. Chem.* **2018**, *130*, 16669–16673; e) S. Doobary, A. T. Sedikides, H. P. Caldora, D. L. Poole, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 1155–1160; *Angew. Chem.* **2020**, *132*, 1171–1176; f) S. Meyer, J. Häfliger, M. Schäfer, J. J. Molloy, C. G. Daniliuc, R. Gilmour, *Angew. Chem. Int. Ed.* **2021**, *60*, 6430–6434; *Angew. Chem.* **2021**, *133*, 6501–6506.
- [16] T. Bykova, N. Al-Maharik, A. M. Z. Slawin, D. O'Hagan, *J. Fluorine Chem.* **2015**, *179*, 188–192.
- [17] a) S. Stavber, B. Sket, B. Zajc, M. Zupan, *Tetrahedron* **1989**, *45*, 6003–6010; b) B. Zajc, M. Zupan, *J. Org. Chem.* **1990**, *55*, 1099–1102.
- [18] J. L. Cotter, L. J. Andrews, R. M. Keefer, *J. Am. Chem. Soc.* **1962**, *84*, 793–797.
- [19] Possible conformations of the reactive complex of olefin **8** with $[p\text{TolIF}]^+$ have been investigated computationally (see inset structure).



- In the thermodynamically preferred complex Cpx B (see the Supporting Information) the I-F distance is slightly shorter than the sum of the Van der Waals radii (3.45 Å). For studies on halogen bonding in I(III) compounds, see: a) G. Cavallo, J. S. Murray, P. Politzer, T. Pilati, M. Ursini, G. Resnatin, *IUCrJ* **2017**, *4*, 411–419; b) F. Heinen, E. Engelage, C. J. Cramer, S. M. Huber, *J. Am. Chem. Soc.* **2020**, *142*, 8633–8640.
- [20] a) A. Granados, A. Villribera, *Molecules* **2020**, *25*, 3264; b) For an example from this laboratory, see E.-M. Tanzer, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Chem. Eur. J.* **2012**, *18*, 2006–2013.
- [21] The Van der Waals volumes were calculated according to: Y. H. Zhao, M. H. Abraham, A. M. Zissimos, *J. Org. Chem.* **2003**, *68*, 7368; Please see A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451.
- [22] 2057761 contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: February 12, 2021

Revised manuscript received: March 12, 2021

Accepted manuscript online: March 15, 2021

Version of record online: May 1, 2021