Photochemistry

DOI: 10.1002/anie.201204080

Synthesis of Fluorinated Tricyclic Scaffolds by Intramolecular [2+2] Photocycloaddition Reactions**

*Diego A. Fort, Thomas J. Woltering, Matthias Nettekoven, Henner Knust, and Thorsten Bach**

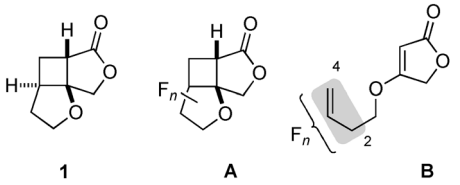
Dedicated to Professor George A. Olah on the occasion of his 85th birthday

In recent years, fluorinated compounds have attracted considerable synthetic interest and they have gained an important position among heteroatom-substituted hydrocarbon analogues.[1] First and foremost, this interest has been kindled by the success that fluorinated compounds have encountered in several areas of medicinal chemistry.[2] Furthermore, many other useful and intriguing properties of fluorinated compounds have been elucidated,[1,3] which has further intensified the efforts towards their selective synthesis. In this regard, it is surprising to note that the use of fluorinated compounds in [2+2] photocycloaddition reactions[4] has not been studied systematically to date. There are scattered reports on the preparation of fluorinated cage compounds and C_6F_{10} valence isomers,[5] on the use of fluorinated ethylenes in intermolecular [2+2] photocycloaddition reactions,[6] and on the synthesis of fluoro- and trifluoromethyl-substituted uracil derivatives.[7] A monofluorinated olefin has recently been used successfully as reaction partner in an intramolecular enone [2+2] photocycloaddition.[8] Apart from that, the use of fluorinated compounds in [2+2] photocycloaddition chemistry has remained essentially unexplored.

Given the potential use of fluorinated compounds as new scaffolds for medicinal chemistry we have now studied a modification of the known tricyclic skeleton **1**[9] by fluorine substitution (Scheme 1). Products of general structure **A** seemed accessible from precursors **B**, in which the carbon atoms at positions 2, 3, and 4 should carry fluorine atoms. Particular interest was directed to the question whether electron-deficient trifluoro-substituted olefins could serve as intramolecular reaction partners in a [2+2] photocycloaddition and whether any facial diastereoselectivity would be exerted by a fluorine atom at the stereogenic center C2. Preliminary results of these studies are disclosed herein.

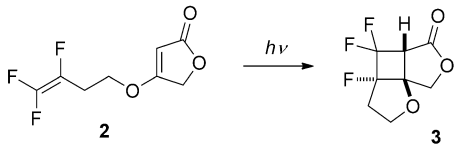
An initial set of experiments was performed with tetronate **2** derived from commercially available 3,4,4-trifluorobut-3-enyl bromide. Despite the fact that the trifluoro-substituted alkene is extremely electron-poor,[10] it did successfully add to the photoexcited tetronate at $\lambda = 254$ nm in isopropanol as the solvent (Table 1, entry 1). A further modification of the solvent revealed that diethyl ether (Table 1, entry 5) was superior to *tert*-butanol (entry 2), dichloromethane (entry 3), or acetonitrile (entry 4). In the latter solvents the reaction remained incomplete after an irradiation time of six hours, while severe product decomposition was found to occur in *tert*-butanol.

The fact that the reaction can be successfully sensitized by acetone (Table 1, entries 6 and 7) at $\lambda = 300$ nm supports the



Scheme 1. Structure of **1**, which is the product of an intramolecular [2+2] photocycloaddition of a tetronate, and of its fluorinated analogues **A**, which are potentially accessible from fluorinated precursors **B**.

Table 1: Optimization of reaction conditions for the intramolecular [2+2] photocycloaddition of tetronate **2** to the tricyclic product **3**.



Entry[a]	λ [nm]	Solvent	t [h][b]	Yield [%][c]
1	254	*i*PrOH	4	24
2	254	*t*BuOH	4	< 5
3	254	CH_2Cl_2	6	53[d]
4	254	MeCN	6	62[e]
5	254	Et_2O	4	78
6	300	acetone	4	14[f]
7	300[g]	acetone	4	11[h]

[a] All reactions were conducted using a RPR-100 reactor with 16 Rayonet RPR-2540 Å lamps or RPR-3000 Å lamps (quartz apparatus) as the irradiation source in deaerated solvent ($c = 5$ mM). [b] Elapsed reaction time to achieve 100% conversion of the starting material. [c] Yield of isolated product after chromatographic purification. [d] The reaction was not complete after 6 h. 25% of starting material was recovered. [e] The reaction was not complete after 6 h. 15% of starting material was recovered. [f] Paternò–Büchi reaction products (41%) were obtained as major products. [g] Duran filter. [h] Paternò–Büchi reaction products (36%) were obtained as major products.

[*] Dr. D. A. Fort, Prof. Dr. T. Bach
Lehrstuhl für Organische Chemie I
Technische Universität München
Lichtenbergstr. 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: http://www.oc1.ch.tum.de/home_en/
Dr. T. J. Woltering, Dr. M. Nettekoven, Dr. H. Knust
Discovery Chemistry, PRCB, F. Hoffmann-La Roche AG
Grenzacherstrasse 124, 4070 Basel (Switzerland)

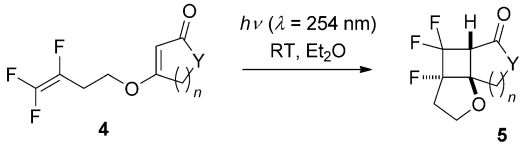
[**] D.A.F. wishes to acknowledge funding by the Roche Postdoc Fellowship (RPF) Program.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204080.

previously postulated intermediacy of a triplet species in the [2+2] photocycloaddition of tetronates.[9b] The major reaction in acetone as the solvent was however the addition of the photoexcited ketone (Paternò–Büchi reaction) to the trifluoro-substituted double bond.

Since there is no precedence for a successful addition reaction of a trifluoro-substituted olefin to a photoexcited enone, it was investigated whether the reaction is feasible with other substrates but tetronates. To this end, the enones **4a** and **4c** (Table 2) were prepared by condensation of the respective 1,3-dicarbonyl compounds with 3,4,4-trifluorobut-3-enol.[11] Tetramate **4b** was synthesized by alkylation of *N*-Boc-protected tetramic acid[12] with the respective bromide and subsequent deprotection using trifluoroacetic acid (TFA; see the Supporting Information).

Table 2: Intramolecular [2+2] photocycloaddition of 3,4,4-trifluorobut-3-enyloxy-substituted enones **4** to the respective trifluorinated products **5**.



4 **5**

Entry[a]	Substrate	*n*	Y	Product	Yield [%][b]
1	**4a**	1	CH_2	**5a**	95
2	**4b**	1	NH	**5b**	75
3	**4c**	2	CH_2	**5c**	83

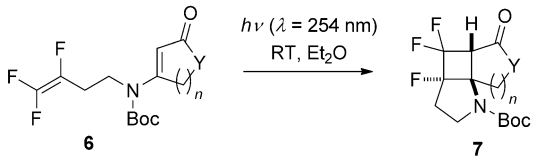
[a] All reactions were conducted using a RPR-100 reactor with 16 Rayonet RPR-2540 Å lamps (quartz apparatus) as the irradiation source in deaerated solvent ($c = 5$ mM). [b] Yield of isolated product after chromatographic purification.

To our delight, the [2+2] photocycloaddition of compounds **4** proceeded equally well under the optimal conditions, which had been established with substrate **2**. Cyclopentenone **4a** delivered the respective tricyclic product **5a** in a yield of 95% (Table 2, entry 1). The tetramic acid derivative **4b** reacted smoothly (Table 2, entry 2) as did the six-membered cyclohexenone **4c** (entry 3). In all cases, the products **5** were obtained as single regio- and diastereoisomers. The relative configuration of the three stereogenic centers was established by NOE studies.

By varying the linker between the enone and the trifluorovinyl group it was checked whether the intramolecular [2+2] photocycloaddition of trifluoroalkenes is generally applicable. The β-amino-substituted enone substrates **6** (Table 3) were prepared by condensation of 3,4,4-trifluorobut-3-enylamine with the respective ketones and subsequent *tert*-butoxycarbonyl (Boc) protection of the secondary amine group (see the Supporting Information). The desired photochemical reaction proceeded cleanly upon irradiation at $\lambda = 254$ nm and delivered products **7** in diastereomerically pure form. The reaction was complete in one hour.

A longer tether between the enone and the olefin was employed in the reaction of substrates **8**, which are homologous to **4a** and **4c** and which were prepared in the same

Table 3: Intramolecular [2+2] photocycloaddition of *N*-Boc-protected 3,4,4-trifluorobut-3-enylamino-substituted enones **6** to the respective trifluorinated products **7**.

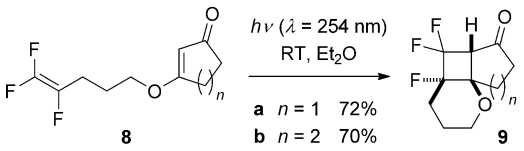


6 **7**

Entry[a]	Substrate	*n*	Y	Product	Yield [%][b]
1	**6a**	1	O	**7a**	73
2	**6b**	1	CH_2	**7b**	69
3	**6c**	2	CH_2	**7c**	68

[a] All reactions were conducted using a RPR-100 reactor with 16 Rayonet RPR-2540 Å lamps (quartz apparatus) as the irradiation source in deaerated solvent ($c = 5$ mM). [b] Yield of isolated product after chromatographic purification.

fashion. Formation of the six-membered tetrahydropyran ring proceeded readily and [2+2]-photocycloaddition products **9** were obtained in 72% and 70% yield (Scheme 2).

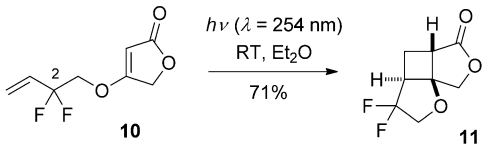


8 **9**

Scheme 2. Intramolecular [2+2] photocycloaddition of 4,5,5-trifluorobut-4-enyloxy-substituted enones **8** to the respective trifluorinated products **9**.

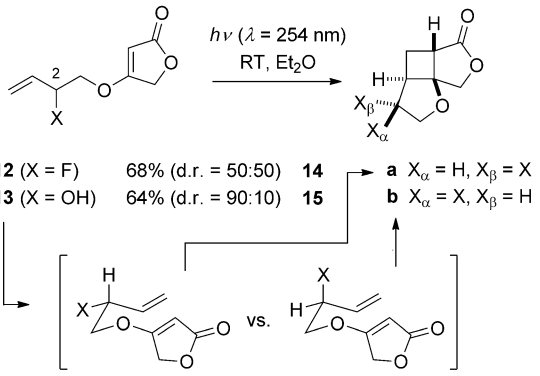
The influence of a difluorosubstitution in position C2 of the side chain was probed with tetronate **10** (Scheme 3). The compound was available from its nonfluorinated analogue[9b] by allylic oxidation and subsequent transformation of the carbonyl group into a difluorinated carbon center. Under the previously established conditions the [2+2] photocycloaddition proceeded smoothly and delivered tricyclic product **11** as a single diastereoisomer in 71% yield.

If a 3-butenyl tetronate with a single fluorine atom in position 2 undergoes a [2+2] photocycloaddition, the question of facial diastereoselectivity arises, because the carbon atom at this position is a stereogenic center. The respective compound **12** (Scheme 4) was prepared from alcohol **13** by treatment with diethylaminosulfur trifluoride (DAST) in dichloromethane as the solvent. Alcohol **13** in turn was prepared by SeO_2 oxidation[13] of 3-butenyl tetronate[9b] (68%

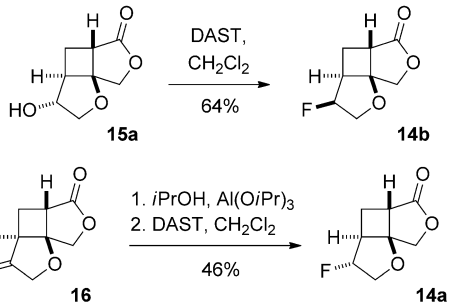


10 **11**

Scheme 3. Intramolecular [2+2] photocycloaddition of 2,2-difluorobut-3-enyl tetronate (**10**) to the respective difluorinated product **11**.



Scheme 4. Facial diastereoselectivity in the intramolecular [2+2] photocycloaddition of 2-fluorobut-3-enyl tetronate (**12**) and 2-hydroxybut-3-enyl tetronate (**13**).



Scheme 5. Diastereoselective preparation of fluoride **14b** and of its diastereoisomer **14a**.

yield). Both compounds were subjected to an intramolecular [2+2] photocycloaddition at $\lambda = 254$ nm in diethyl ether as the solvent. The conversion was complete after five hours and the reaction delivered two diastereoisomeric products **14** and **15** in either case. While the reaction of fluorinated substrate **12** was unselective (d.r. = **14a**/**14b** = 50:50), alcohol **13** delivered a major product, to which structure **15a** was assigned based on extensive one- and two-dimensional NMR spectroscopy studies.

An interpretation of this outcome is relatively straightforward when considering the favored conformation for either substrate (Scheme 4). If the heteroatom substituent X is in a pseudoequatorial position (depicted on the bottom left) product diastereoisomers **a** will be formed. If it is positioned pseudoaxially (bottom right) the diastereoisomers **b** will be the products.

Apparently, the small fluorine atom (X = F) does not exhibit a preference for either position and the conformations are populated equally. As a consequence, products **14** are obtained in a ratio of 1:1. In the case of the alcohol (X = OH), the conformation with a pseudoequatorial hydroxy group is favored and leads via the respective 1,4-biradical[14] to product **15a**. Stereoelectronic effects do not seem to play a role in the stereodifferentiation process.

Access to diastereomerically pure monofluorinated photocycloaddition products was achieved by conventional substitution reactions, which proceeded stereospecifically under inversion of configuration. The major diastereoisomer **15a** obtained from the [2+2] photocycloaddition of alcohol **13** was converted with DAST into monofluorinated product **14b** (Scheme 5).

In an analogous fashion its diastereoisomer **14a** was synthesized. Access to ketone **16** was possible either by oxidation of products **15** or—in low yields—by direct [2+2] photocycloaddition of a 2-oxo-3-butenyl tetronate. The Meerwein–Ponndorf–Verley reduction[15] of this ketone proceeded chemo- and diastereoselectively to alcohol **15b** (62% yield), which in turn was converted to monofluoride **14a** by treatment with DAST (74%).

In summary, it was shown that fluorinated scaffolds of general type **A** can be generated by an intramolecular [2+2] photocycloaddition reaction of appropriately substituted tetronates. Regarding the use of fluorinated compounds in this type of chemistry, the most significant results are:

1) The electron-withdrawing character of fluorine atoms that are directly attached to a double bond does not impair the ability of the double bond to undergo an enone photocycloaddition reaction. Under optimized reaction conditions, trifluoro-substituted olefins linked to an enone chromophore smoothly underwent the desired reaction in yields of 68–95%.
2) Fluorine substitution in a position adjacent to a double bond is compatible with intramolecular [2+2] photocycloaddition chemistry. Both difluoro- and monofluoro-substituted substrates **10** and **12** reacted cleanly.
3) A fluoro-substituted stereogenic center in α-position to an olefin does not induce a notable facial diastereoselectivity. As observed in other photochemical processes,[16] stereoelectronic effects have a minor impact on the facial diastereoselectivity. In thermal reactions, however, they often govern the facial diastereoselectivity in acylic substrates.[17]

The compatibility of fluorine substitution with typical [2+2] photocycloaddition chemistry, as shown in this study, is expected to stimulate future work towards the preparation of cyclobutane-based fluorinated scaffolds. Research along these lines continues in our laboratories.

Received: May 25, 2012
Revised: August 3, 2012
Published online: September 7, 2012

Keywords: cycloaddition · diastereoselectivity · fluorine · photochemistry · strained molecules

[1] a) T. Hiyama, *Organofluorine Compounds*, Springer, Berlin, **2010**; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; c) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; d) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

[2] a) F. M. D. Ismail, *J. Fluorine Chem.* **2002**, *118*, 27–33; b) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; c) J. P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–

1012; d) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013 – 1029; e) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303 – 319; f) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; g) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; h) A. K. Podichetty, S. Wagner, S. Schröer, A. Faust, O. Schober, M. Schäfers, K. Kopka, G. Haufe, *J. Med. Chem.* **2009**, *52*, 3484 – 3495.

[3] a) *Fluorinated Heterocyclic Compounds* (Ed.: V. A. Petrov), Wiley, Hoboken, **2009**; b) S. Fustero, J. F. Sanz-Cervera, J. L. Aceña, M. Sánchez-Roselló, *Synlett* **2009**, 525 – 549; c) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem.* **2011**, *123*, 12062 – 12074; *Angew. Chem. Int. Ed.* **2011**, *50*, 11860 – 11871.

[4] Reviews: a) J. P. Hehn, C. Müller, T. Bach in *Handbook of Synthetic Photochemistry* (Eds.: A. Albini, M. Fagnoni), Wiley-VCH, Weinheim, **2009**, pp. 171 – 215; b) S. A. Fleming in *Molecular and Supramolecular Photochemistry*, *Vol. 12* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**, pp. 141 – 160; c) P. Margaretha in *Molecular and Supramolecular Photochemistry*, *Vol. 12* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**, pp. 211 – 237; d) J. P. Pete in *CRC Handbook of Organic Photochemistry and Photobiology*, *2nd ed.* (Eds.: W. Horspool, F. Lenci), CRC, Boca Raton, **2004**, pp. 71/1 – 71/14; e) T. Bach, *Synthesis* **1998**, 683 – 703; f) J.-P. Pete, *Adv. Photochem.* **1996**, *21*, 135 – 216; g) J. Mattay, R. Conrads, R. Hoffmann in *Methoden der Organischen Chemie (Houben-Weyl) 4te Aufl.*, Band E 21c (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 3085 – 3132; h) M. T. Crimmins, T. L. Reinhold, *Org. React.* **1993**, *44*, 297 – 588.

[5] a) W. P. Dailey, D. M. Lemal, *J. Am. Chem. Soc.* **1984**, *106*, 1169 – 1170; b) R. A. Correa, N. Jing, *J. Org. Chem.* **1993**, *58*, 6406 – 6409.

[6] a) H. Kimoto, K. Takahashi, H. Muramatsu, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 764 – 769; b) D. Andrew, D. J. Hastings, A. C. Weedon, *J. Am. Chem. Soc.* **1994**, *116*, 10870 – 10882.

[7] a) A. J. Wexler, J. S. Swenton, *J. Am. Chem. Soc.* **1976**, *98*, 1602 – 1604; b) A. J. Wexler, R. J. Balchunis, J. S. Swenton, *J. Org. Chem.* **1984**, *49*, 2733 – 2738; c) T. Iwaoka, N. Katagiri, M. Sato, C. Kaneko, *Chem. Pharm. Bull.* **1992**, *40*, 2319 – 2324; d) C. Gauzy, B. Saby, E. Pereira, S. Faure, D. J. Aitken, *Synlett* **2006**, 1394 – 1398.

[8] A. N. Tkachenko, D. S. Radchenko, P. K. Mykhailiuk, O. O. Grygorenko, I. V. Komarov, *Org. Lett.* **2009**, *11*, 5674 – 5676.

[9] Selected references: a) M. Kemmler, T. Bach, *Angew. Chem.* **2003**, *115*, 4973 – 4975; *Angew. Chem. Int. Ed.* **2003**, *42*, 4824 – 4826; b) M. Kemmler, T. Bach, *Eur. J. Org. Chem.* **2004**, 4582 – 4595; c) M. Fleck, C. Yang, T. Wada, Y. Inoue, T. Bach, *Chem. Commun.* **2007**, 822 – 824; d) M. Fleck, T. Bach, *Chem. Eur. J.* **2010**, *16*, 6015 – 6032; e) J. P. Hehn, D. Gamba-Sánchez, M. Kemmler, M. Fleck, B. Basler, T. Bach, *Synthesis* **2010**, 2308 – 2312; f) R. Weixler, J. P. Hehn, T. Bach, *J. Org. Chem.* **2011**, *76*, 5924 – 5935.

[10] The electrophilic epoxidation of fluorinated olefins, for example, is notoriously difficult to achieve. For some references, see: a) M. M. Kremlev, I. S. Mazny, Y. L. Yagupolskii, *J. Fluorine Chem.* **1991**, *54*, 100; b) T. I. Gorbunova, A. Y. Zapevalov, V. I. Saloutin, *Russ. Chem. Bull.* **1995**, *44*, 1470 – 1473; c) A. Arnone, D. D. DesMareau, B. Novo, V. A. Petrov, M. Pregnolato, G. Resnati, *J. Org. Chem.* **1996**, *61*, 8805 – 8810.

[11] Y. Tada, M. Sato, N. Takeno, Y. Nakacho, K. Shigehara, *Makromol. Chem.* **1993**, *194*, 2163 – 2171.

[12] W. R. Li, S. T. Lin, N.-M. Hsu, M. S. Chern, *J. Org. Chem.* **2002**, *67*, 4702 – 4706.

[13] G. R. Waitkins, C. W. Clark, *Chem. Rev.* **1945**, *36*, 235 – 289.

[14] D. I. Schuster, G. N. Lem, A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3 – 22.

[15] a) H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, *444*, 221 – 238; b) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, *37*, 537; c) W. Ponndorf, *Angew. Chem.* **1926**, *39*, 138 – 143; d) J. Yin, M. A. Huffman, K. M. Conrad, J. D. Armstrong III, *J. Org. Chem.* **1996**, *61*, 8805 – 8810.

[16] For the lack of facial diastereoselectivity in the Paternò–Büchi reaction of α-chiral carbonyl compounds, see: a) S. Jarosz, A. Zamojski, *Tetrahedron* **1982**, *38*, 1453 – 1456; b) S. L. Schreiber, *Science* **1985**, *227*, 857 – 863; c) C. Žagar, H.-D. Scharf, *Chem. Ber.* **1991**, *124*, 967 – 969.

[17] a) A. G. O'Brien, *Tetrahedron* **2011**, *67*, 9639 – 9667; b) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191 – 1223.

