Application of 1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes in Diels–Alder Reactions: Synthesis of *ortho*-CF_2Br-Substituted Biaryls

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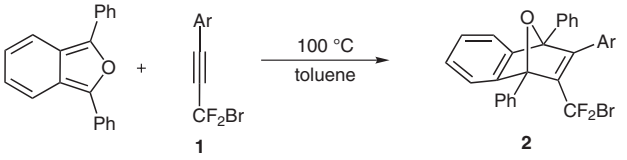
Abstract: 1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes were found to be good dienophiles in Diels–Alder reactions. Based on this key reaction a new pathway towards biaryls with an *ortho*-CF_2Br group was elaborated.

Key words: alkynes, biaryls, bicyclic compounds, Diels–Alder reaction, fluorine

The Diels–Alder reaction[1] is one of the fundamental transformations in organic synthesis providing a broad variety of cyclohexene derivatives leading to the development of a rich downstream chemistry.[2] A variety of fluorinated compounds were prepared using this methodology.[3] Two strategies are suitable, either placing a fluorine substituent in the diene[4] or in the dienophile.[3,5] Moreover, trifluoromethylated or perfluoroalkylated starting materials can be applied.[6] Several [4+2] cycloaddition reactions of 1,3-dienes with 1-(3,3,3-trifluoroprop-1-ynyl)benzene, which are similar to those described in this paper have been executed.[7]

Our interest was focused on the application of the Diels–Alder strategy for the preparation of biaryls. Historically, the first method for the preparation of these compounds was the well-known Ulmann reaction.[8] Nowadays, substitutive aryl–aryl coupling reactions, such as the Suzuki[9] or the Stille[10] coupling, are the most general synthetic routes towards such molecules. However, active halogen atoms in the side chains might be incompatible with the reaction conditions. Thus, we were interested to develop a new pathway towards this important group of compounds. Biaryls are present in a variety of biologically active compounds, which have demonstrated activity across many therapeutic classes, including anti-inflammatory, antirheumatic, and antitumor agents.[11] In addition, some *ortho*-substituted biphenyl homologues have been proposed as potential mimetics of a protein α-helix.[12] Furthermore, it is well known that fluorine substituents in organic compounds change the physicochemical properties[13] as well as the biological activity compared to the fluorine-free parent compounds.[14]



1 2

Scheme 1 Reactions of acetylenes **1** with 1,3-diphenylisobenzofuran

Table 1 Reactions of Acetylenes **1** with 1,3-Diphenylisobenzofuran

Entry	**1**	Ar	Time (h)	Yield of **2** (%)
1	**a**	4-$O_2NC_6H_4$	4	72
2	**b**	4-ClC_6H_4	36	95
3	**c**	Ph	100	83
4	**d**	3-$O_2NC_6H_4$	8	87
5	**e**	2-$O_2NC_6H_4$	8	–
6	**f**	4-$MeOC_6H_4$	170	–

1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes **1**, which were obtained by a catalytic olefination reaction,[15,16] are particularly interesting. They are expected to be good dienophiles because of the strong electron withdrawing effect of the CF_2Br group. On the other hand, there is a principal possibility of further modification of the formed Diels–Alder adducts by reduction or substitution of the bromine atom in the CF_2Br group. Consequently, Diels–Alder reactions of 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzenes **1** represent interesting transformations.

The very reactive 1,3-diphenylisobenzofuran, which is a stabilized *o*-quinodimethane[17] reacted smoothly with the above mentioned acetylenes **1** and gave the expected Diels–Alder adducts **2** in high yields (Scheme 1, Table 1). In contrast, the reactions of 1,3-diphenylisobenzofuran with acetylenes **1e** and **1f** led to complex mixtures of unidentified products.

It is well known that the activity of dienophiles depends strongly on the electronic properties of substituents at the

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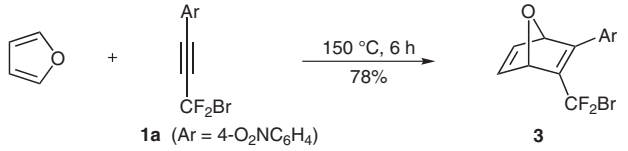
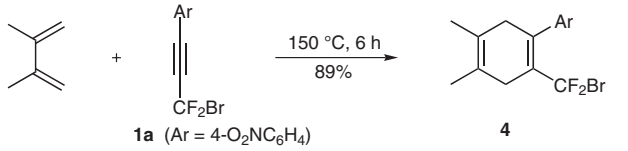
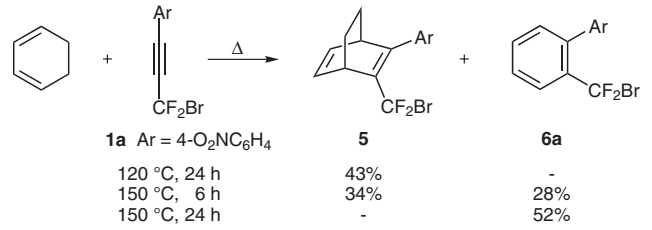


Scheme 2 Reaction of **1a** with furan



Scheme 3 Reaction of **1a** with 2,3-dimethylbutadiene



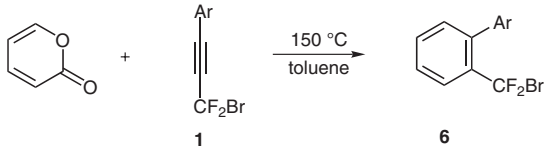
Scheme 4 Reaction of **1a** with cyclohexa-1,3-diene

multiple bonds. Thus, for less reactive dienes such as furan more reactive dienophiles have to be applied. The most active dienophiles in Diels–Alder reactions with normal electron demand contain strong electron-withdrawing groups. Consequently, we first investigated the nitro-substituted acetylene **1a**, which should be the most active among the acetylenes under consideration. Even for this acetylene quite harsh conditions were needed for successful cycloaddition with common dienes. The reaction with furan was complete at 150 °C within 6 hours, giving the oxanorbornadiene derivative **3** in high yield (Scheme 2). The corresponding reaction of 1-(3,3,3-trifluoroprop-1-ynyl)benzene with furan is described to give a complex mixture of products containing an oxanorbornadiene formed by successive Diels–Alder and retro-Diels–Alder reactions.[18]

The reaction of **1a** with 2,3-dimethylbutadiene at 150 °C led to the corresponding Diels–Alder adduct **4** in high yield (Scheme 3).

Surprisingly, the reaction of **1a** with cyclohexa-1,3-diene gave a mixture of two products. The expected Diels–Alder adduct **5** was accompanied by the biaryl **6a** after heating for 6 hours at 150 °C. At 120 °C, the reaction was incomplete after 24 hours and compound **5** was the sole product, while after continued heating at 150 °C for 24 hours, only **6a** was isolated (Scheme 4). The formation of the unexpected product **6a** can be explained by formal extrusion of ethylene from the adduct **5** by retro-Diels–Alder reaction.

The reactions of **1a** with cyclopentadiene and Danishefsky's diene were also investigated. But unfortunately, these dienes did not react at 120 °C and gave only tars at higher temperatures.



Scheme 5 Reactions of acetylenes **1** with 2-pyrone

Subsequently, we examined the reactivity of other acetylenes. The rate of reactions of **1b** and **1c** with furan, 2,3-dimethylbutadiene, and cyclohexa-1,3-diene dropped dramatically. Even after a longer reaction time the starting materials were not completely consumed. Moreover, the formation of complex mixtures and considerable amount of tars was observed.

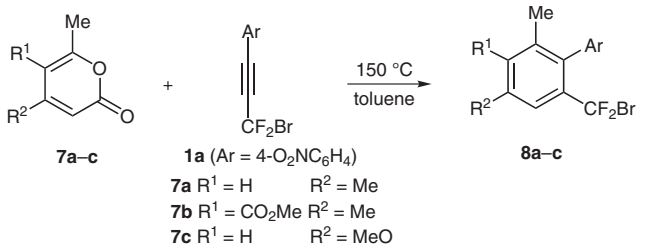
Our further investigations were focused on the application of acetylenes **1** for the synthesis of biaryls. Diels–Alder reactions of 2-pyrones with acetylenes are known to lead to thermolabile cycloadducts, which easily extrude carbon dioxide to give biaryls at elevated temperature.[19] Substituted biaryls are central components of fine chemicals for a diverse range of applications. In particular, pharmaceuticals and herbicides with biaryl substructures are of general interest.[20] In addition, biaryls were applied as chiral ligands in catalysis, as liquid crystals, or organic conductors.[21]

Initially, we investigated reactions of the unsubstituted 2-pyrone with acetylenes **1**, bearing a nitro group in different positions of the aryl ring. The acetylenes **1a** and **1d** reacted with 2-pyrone at 150 °C in toluene giving the desired biaryls **6a** and **6d** in good yields (Scheme 5, Table 2). In the case of the 2-nitrophenyl acetylene **1e** the yield dropped dramatically, obviously because of steric hindrance in the transition state of the cycloaddition.

The reactions of three more 2-pyrones **7a–c** with acetylenes were also examined. We found that the 2-pyrones **7a** and **7b** gave the corresponding biaryls **8a** and **8b**, respectively, in moderate yields. Compared to the unsubstituted 2-pyrone longer reaction times were needed for complete consumption of the starting materials. After heating for 4 days, we still found starting materials in both cases. Extending the reaction time to one week led to completion and the yield of biaryl **8b** rose to 40%. In contrast to 2-pyrone **7a**, the yield of biaryl **8a** dropped to trace amounts because of sudden tarring of the reaction mixture. The reaction of pyrone **7c** with acetylene **1a** was not successful, probably because of decomposition of pyrone **7c** at high temperature; only traces of **8c** were found (Scheme 6, Table 3).

Table 2 Synthesis of Biaryls **6**

Entry	**1**	Ar	Time (h)	Yield of **6** (%)
1	**a**	4-$O_2NC_6H_4$	53	76
2	**d**	3-$O_2NC_6H_4$	70	72
3	**e**	2-$O_2NC_6H_4$	70	22



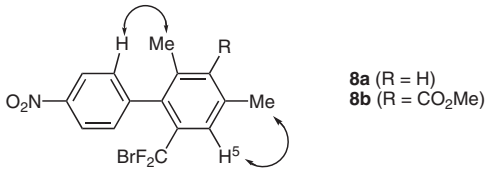
7a–c **1a** (Ar = 4-$O_2NC_6H_4$) **8a–c**

7a R^1 = H R^2 = Me
7b R^1 = CO_2Me R^2 = Me
7c R^1 = H R^2 = MeO

Scheme 6 Reactions of acetylenes **1a** with 2-pyrones **7**

Table 3 Synthesis of Biaryls **8a–c**

Entry	2-Pyrone	Time (d)	Product	Yield (%)
1	**7a**	4	**8a**	17
2	**7a**	7	**8a**	traces
3	**7b**	4	**8b**	20
4	**7b**	7	**8b**	40
5	**7c**	4	**8c**	traces



8a (R = H)
8b (R = CO_2Me)

Figure 1 Observed NOEs in compound **8a**

The configuration of the biaryls **8a** and **8b** was determined by nuclear Overhauser effect (NOE) experiments. Irradiation of the *ortho*-proton of the 4-nitrophenyl ring caused increase of the singlets of one of the methyl groups in **8a** and **8b**, while irradiation of the H^5 frequency increased the singlet of the other methyl group of compound **8a** (Figure 1).

In summary, we have investigated the reactions of 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzenes **1** with a series of active dienes such as 1,3-diphenylisobenzofuran, furan, 2,3-dimethylbutadiene, and cyclohexa-1,3-diene. Also a new approach to biaryls, containing a CF_2Br group in *ortho*-position was elaborated using the Diels–Alder reaction of pyrones with **1** as the key step.

NMR spectra were recorded on Bruker ARX 300, Bruker AMX 400, and Varian Inova 500 MHz spectrometers in $CDCl_3$ with TMS and CCl_3F as internal standards. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltonics. Column and TLC chromatography were performed on silica gel Merck 60 or Merck $60F_{254}$ plates, respectively. All dienes were distilled before use.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes
The 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzenes **1** were synthesized according to previously reported procedures.[16d] Reactions were carried out in 20 mmol scale. ^1H and ^{19}F NMR data of compounds **1b**,**1f** are in agreement with literature values.[16d]

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-4-nitrobenzene (1a)
Yield: 4.14 g (75%); yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.9 Hz, 2 H), 8.28 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.2 (t, *J* = 39.1 Hz, C≡*C*CF_2Br), 86.9 (t, *J* = 5.8 Hz, *C*≡CCF_2Br), 101.6 (t, *J* = 289.8 Hz, CF_2Br), 123.9, 133.3, 140.1 (t, *J* = 7.6 Hz), 148.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –33.41 (s, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_9H_4BrF_2NO_2$ + Na [M^+ + Na]: 297.9291; found: 297.9293.

Anal. Calcd for $C_9H_4BrF_2NO_2$: C, 39.16; H, 1.46. Found: C, 39.31; H, 1.52.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-4-chlorobenzene (1b)
Yield: 3.82 g (71%); colorless oil.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzene (1c)
Yield: 2.96 g (64%); colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.2 Hz, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.51 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.0 (t, *J* = 38.3 Hz, C≡*C*CF_2Br), 90.0 (t, *J* = 5.8 Hz, *C*≡CCF_2Br), 102.1 (t, *J* = 289.3 Hz, CF_2Br), 118.8, 128.7, 130.9, 132.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –31.22 (s, CF_2Br).

Anal. Calcd for $C_9H_5BrF_2$: C, 46.79; H, 2.18. Found: C, 46.92; H, 2.25.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-3-nitrobenzene (1d)
Yield: 3.92 g (71%); yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (t, *J* = 8.0 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.34 (d, *J* = 8.0 Hz, 1 H), 8.41 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.3 (t, *J* = 39.1 Hz, C≡*C*CF_2Br), 86.6 (t, *J* = 5.6 Hz, *C*≡CCF_2Br), 101.6 (t, *J* = 290.2 Hz, CF_2Br), 125.5, 127.0, 130.0, 135.3 (t, *J* = 7.4 Hz), 137.8, 148.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –33.20 (s, CF_2Br).

Anal. Calcd for $C_9H_4BrF_2NO_2$: C, 39.16; H, 1.46. Found: C, 39.39; H, 1.57.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-2-nitrobenzene (1e)
Yield: 3.09 g (56%); yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.80 (m, 3 H), 8.22 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.0 (t, *J* = 6.3 Hz, C≡*C*CF_2Br), 86.3 (t, *J* = 39.1 Hz, *C*≡CCF_2Br), 101.8 (t, *J* = 290.1 Hz, CF_2Br), 125.2, 131.7, 133.7, 135.4, 138.2, 149.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –33.51 (s, CF_2Br).

Anal. Calcd for $C_9H_4BrF_2NO_2$: C, 39.16; H, 1.46. Found: C, 39.28; H, 1.50.

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-4-methoxybenzene (1f)
Yield: 3.55 g (68%); colorless oil.

Cycloaddition of the 1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes 1 with 1,3-Diphenylisobenzofuran; General Procedure
A solution of the corresponding 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzene **1** (2 mmol) and 1,3-diphenylisobenzofuran (550 mg, 2.05 mmol) in toluene (2 mL) was heated in a sealed glass tube with a Young-tap at 100 °C for an appropriate time. Toluene was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 20:1).

2-[Bromo(difluoro)methyl]-3-(4-nitrophenyl)-1,4-diphenyl-1,4-dihydro-1,4-epoxynaphthalene (2a)
Obtained from **1a** by heating with 1,3-diphenylisobenzofuran at 100 °C for 4 h; yield: 786 mg (72%); white crystals; mp 147–148 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.7 Hz, 2 H), 7.18–7.24 (m, 2 H), 7.32–7.40 (m, 5 H), 7.43–7.60 (m, 4 H), 7.83–7.88 (m, 1 H), 8.06 (d, *J* = 7.6 Hz, 2 H), 8.11 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 92.7 (C–O), 94.7 (C–O), 115.3 (t, *J* = 303.9 Hz, CF_2Br), 121.5, 122.5, 123.7, 126.6, 126.7, 127.9, 128.86, 128.91, 129.2, 129.3 (all CH), 132.9, 134.0, 139.8, 148.1, 148.2, 149.9 (t, *J* = 22.9 Hz, *C*–CF_2Br), 150.3, 156.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –38.38 (d, *J* = 162.1 Hz, 1 F, CF_2Br), –42.43 (d, *J* = 162.1 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{29}H_{18}BrF_2NO_3$ + Na [M^+ + Na]: 568.0330; found: 568.0314.

2-[Bromo(difluoro)methyl]-3-(4-chlorophenyl)-1,4-diphenyl-1,4-dihydro-1,4-epoxynaphthalene (2b)
Obtained from **1b** by heating with 1,3-diphenylisobenzofuran at 100 °C for 36 h; yield: 1.018 g (95%); white crystals; mp 62–63 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.4 Hz, 2 H), 7.11–7.19 (m, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.30–7.48 (m, 7 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.81 (d, *J* = 7.1 Hz, 1 H), 8.06 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 92.0 (C–O), 94.0 (C–O), 115.3 (t, *J* = 304.0 Hz, CF_2Br), 121.0, 121.7, 127.4, 127.6, 128.2, 128.25, 128.27, 128.4, 128.6, 128.8 (all CH), 130.7, 132.8, 133.9, 134.6, 147.7 (t, *J* = 22.4 Hz, *C*–CF_2Br), 148.1, 150.0, 157.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –37.41 (d, *J* = 160.3 Hz, 1 F, CF_2Br), –41.74 (d, *J* = 160.3 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{29}H_{18}BrClF_2O$ + Na [M^+ + Na]: 557.0096; found: 557.0090.

Anal. Calcd for $C_{29}H_{18}BrClF_2O$: C, 65.01; H, 3.39. Found: C, 65.09; H, 3.28.

2-[Bromo(difluoro)methyl]-3-phenyl-1,4-diphenyl-1,4-dihydro-1,4-epoxynaphthalene (2c)
Obtained from **1c** by heating with 1,3-diphenylisobenzofuran at 100 °C for 100 h; yield: 832 mg (83%); viscous oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.88–7.77 (m, 17 H), 8.02–8.06 (m, 1 H), 8.11–8.15 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 94.2 (C–O), 94.7 (C–O), 115.5 (t, *J* = 303.8 Hz, CF_2Br), 125.8, 125.8, 126.6, 127.1, 127.3, 127.5, 127.6, 127.9, 128.0, 128.2, 128.4, 128.7, 128.9 (all CH), 133.1, 134.1, 135.0, 148.5, 147.1 (t, *J* = 22.6 Hz, *C*–CF_2Br), 150.2, 158.5.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –37.47 (d, *J* = 159.3 Hz, 1 F, CF_2Br), –41.54 (d, *J* = 159.3 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{29}H_{19}BrF_2O$ + Na [M^+ + Na]: 525.0463; found: 525.0451.

2-[Bromo(difluoro)methyl]-3-(3-nitrophenyl)-1,4-diphenyl-1,4-dihydro-1,4-epoxynaphthalene (2d)
Obtained from **1d** by heating with 1,3-diphenylisobenzofuran at 100 °C for 8 h; yield: 950 mg (87%); viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.24 (m, 3 H), 7.30–7.51 (m, 8 H), 7.55 (d, *J* = 7.4 Hz, 2 H), 7.73 (br s, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 2 H), 8.13 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 92.7 (C–O), 94.6 (C–O), 115.4 (t, *J* = 303.9 Hz, CF_2Br), 121.5, 122.4, 122.8, 123.8, 126.7, 127.8, 127.9, 128.85, 128.9, 129.2, 129.3, 129.6 (all CH), 132.9, 134.0, 134.5, 135.6, 148.2, 149.8 (t, *J* = 22.9 Hz, *C*–CF_2Br), 150.3, 156.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –38.45 (d, *J* = 163.0 Hz, 1 F, CF_2Br), –42.50 (d, *J* = 163.0 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{29}H_{18}BrF_2NO_3$ + Na [M^+ + Na]: 568.0330; found: 568.0333.

Cycloaddition of the 1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes 1 with Dienes; General Procedure
The corresponding 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzene **1** (1 mmol) and the corresponding diene (1.5 mL) were heated in a sealed glass tube with a Young-tap. The excess of the diene was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 20:1).

2-[Bromo(difluoro)methyl]-3-(4-nitrophenyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (3)
Obtained from **1a** by heating with furan at 150 °C for 6 h; yield: 268 mg (78%); white crystals; mp 117–119 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.63 (m, 1 H), 5.67–5.70 (m, 1 H), 7.24 (dd, *J* = 5.3, 1.8 Hz, 1 H), 7.43–7.48 (m, 3 H), 8.27 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 86.4 (CH–O), 89.9 (CH–O), 118.3 (t, *J* = 300.1 Hz, CF_2Br), 125.8, 130.1, 142.4, 146.2, 136.4 (t, *J* = 15.3 Hz, *C*–CF_2Br), 140.1, 149.9, 153.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –39.92 (d, *J* = 159.2 Hz, 1 F, CF_2Br), –47.92 (d, *J* = 159.2 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{13}H_8BrF_2NO_3$ + Na [M^+ + Na]: 388.9454; found: 388.9443.

Anal. Calcd for $C_{13}H_8BrF_2NO_3$: C, 45.37; H, 2.34; N, 4.07. Found: C, 45.55; H, 2.21; N, 4.03.

1-{2-[Bromo(difluoro)methyl]-4,5-dimethylcyclohexa-1,4-dien-1-yl}-4-nitrobenzene (4)
Obtained from **1a** by heating with 2,3-dimethylbutadiene at 150 °C for 6 h; yield: 319 mg (89%); white solid; mp 72–73 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3), 2.83 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.02 (t, *J* = 7.2 Hz, 2 H, CH_2), 7.37 (d, *J* = 8.7 Hz, 2 H), 8.22 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 18.0 (CH_3), 26.9 (CH_2), 42.0 (CH_2), 121.7, 122.1, 123.6, 127.8, 118.3 (t, *J* = 307.3 Hz, CF_2Br), 129.4 (t, *J* = 19.4 Hz, *C*–CF_2Br), 136.1 (t, *J* = 3.5 Hz), 147.0, 148.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –41.79 (s, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{15}H_{14}BrF_2NO_2$ + Na [M^+ + Na]: 380.0074; found: 380.0069.

Anal. Calcd for $C_{15}H_{14}BrF_2NO_2$: C, 50.30; H, 3.94; N, 3.91. Found: C, 50.27; H 3.95; N, 3.96.

2-[Bromo(difluoro)methyl]-3-(4-nitrophenyl)bicyclo[2.2.2]octa-2,5-diene (5)
Obtained from **1a** by heating with cyclohexa-1,3-diene at 120 °C for 24 h; yield: 153 mg (43%);

white solid; mp 55–57 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.74 (m, 4 H, CH_2), 3.72–3.78 (m, 1 H, CH), 3.96–4.02 (m, 1 H, CH), 6.48 (td, *J* = 6.6, 1.3 Hz, 1 H, CH=CH), 6.56 (td, *J* = 6.6, 1.3 Hz, 1 H, CH=CH), 7.39 (d, *J* = 8.7 Hz, 2 H), 8.20 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (CH_2), 25.2 (CH_2), 38.2 (CH), 45.7 (CH), 117.0 (t, *J* = 304.9 Hz, CF_2Br), 123.3, 128.5, 133.6, 134.5 (all CH), 138.1 (t, *J* = 21.0 Hz, *C*–CF_2Br), 144.3, 145.4, 147.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –42.73 (d, *J* = 149.0 Hz, 1 F, CF_2Br), –43.96 (d, *J* = 149.0 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{15}H_{12}BrF_2NO_2$ + Na [M^+ + Na]: 377.9912; found: 377.9921.

2-[Bromo(difluoro)methyl]-4′-nitro-1,1′-biphenyl (6a)
Obtained from **1a** by heating with cyclohexa-1,3-diene at 150 °C for 24 h; yield: 171 mg (52%); yellow crystals; mp 75–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.28 (m, 1 H), 7.51–7.61 (m, 4 H), 7.71–7.78 (m, 1 H), 8.28 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.1 (t, *J* = 305.8 Hz, CF_2Br), 122.9, 125.3 (t, *J* = 7.0 Hz), 128.7, 130.4, 131.2, 131.7, 135.6 (t, *J* = 21.6 Hz, *C*–CF_2Br), 137.3, 146.8, 147.4.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –39.30 (s, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{13}H_8BrF_2NO_2$ + Na [M^+ + Na]: 349.9604; found: 349.9605.

Anal. Calcd for $C_{13}H_8BrF_2NO_2$: C, 47.59; H, 2.46; N, 4.27. Found: C, 47.59; H, 2.28; N, 4.21.

Cycloaddition of the 1-(3-Bromo-3,3-difluoroprop-1-ynyl)benzenes 1 with 2-Pyrones; General Procedure
The corresponding 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzene (1 mmol) and the corresponding 2-pyrone (1.05 mmol) in anhyd toluene (1 mL) were heated in a sealed glass tube with a Young-tap at 150 °C during appropriate time. Toluene was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 20:1).

2-[Bromo(difluoro)methyl]-4′-nitro-1,1′-biphenyl (6a)
Obtained from **1a** by heating with 2-pyrone at 150 °C for 53 h; yield: 249 mg (76%). Data see above.

2-[Bromo(difluoro)methyl]-3′-nitro-1,1′-biphenyl (6d)
Obtained from **1d** by heating with 2-pyrone at 150 ° for 70 h; yield: 236 mg (72%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 7.0, 1.9 Hz, 1 H), 7.51–7.66 (m, 3 H), 7.70–7.78 (m, 2 H), 8.24–8.30 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.6 (t, *J* = 305.8 Hz, CF_2Br), 123.1, 124.8, 125.6 (t, *J* = 7.0 Hz), 129.0, 129.1, 131.7, 132.5, 135.9, 136.1 (t, *J* = 21.6 Hz, *C*–CF_2Br), 138.2, 141.9, 148.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –39.51 (s, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{13}H_8BrF_2NO_2$ + Na [M^+ + Na]: 349.9599; found: 349.9595.

2-[Bromo(difluoro)methyl]-2′-nitro-1,1′-biphenyl (6e)
Obtained from **1d** by heating with 2-pyrone at 150 °C for 70 h; yield: 72 mg (22%); yellow crystals; mp 58–59 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 6.4, 1.9 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.49–7.61 (m, 4 H), 7.66 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.72 (dd, *J* = 7.0, 1.9 Hz, 1 H), 8.16 (dd, *J* = 8.2, 0.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 117.4 (t, *J* = 305.7 Hz, CF_2Br), 124.5, 125.3 (t, *J* = 6.7 Hz), 128.3, 129.1, 130.7, 131.0, 132.3, 132.5, 134.5, 134.8 (t, *J* = 21.7 Hz, *C*–CF_2Br), 135.2, 148.0.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –40.74 (d, *J* = 159.5 Hz, 1 F, CF_2Br), –41.31 (d, *J* = 159.5 Hz, 1 F, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{13}H_8BrF_2NO_2$ +Na [M^+ + Na]: 349.9604; found: 349.9599.

Anal. Calcd for $C_{13}H_8BrF_2NO_2$: C, 47.59; H, 2.46; N, 4.27. Found: C, 47.69; H, 2.47; N, 4.07.

2-[Bromo(difluoro)methyl]-4,6-dimethyl-4′-nitro-1,1′-biphenyl (8a)
Obtained from **1a** by heating with 2-pyrone **7a** at 150 °C for 4 d; yield: 61 mg (17%); viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 7.25 (s, 1 H), 7.39 (s, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 8.29 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (CH_3), 21.2 (CH_3), 117.3 (t, *J* = 305.2 Hz, CF_2Br), 123.1 (t, *J* = 7.6 Hz), 123.2, 130.9, 133.9, 135.7 (t, *J* = 20.8 Hz, *C*–CF_2Br), 137.8, 138.4, 145.6, 147.2.

ESI-MS: *m*/*z* calcd for $C_{15}H_{12}BrF_2NO_2$ + Na [M^+ + Na]: 377.9912; found: 377.9915.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –39.37 (s, CF_2Br).

Methyl 6-[Bromo(difluoro)methyl]-2,4-dimethyl-4′-nitro-1,1′-biphenyl-3-carboxylate (8b)
Obtained from **1a** by heating with 2-pyrone **7b** at 150 °C for 7 d; yield: 166 mg (40%); yellowish crystals; mp 88–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.89 (s, 3 H, CO_2CH_3), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.38 (s, 1 H), 8.23 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (CH_3), 19.6 (CH_3), 52.5 (CO_2CH_3), 116.6 (t, *J* = 306.2 Hz, CF_2Br), 123.3, 124.1 (t, *J* = 7.4 Hz), 130.9, 134.5, 134.6, 135.3, 136.4 (t, *J* = 21.3 Hz, *C*–CF_2Br), 137.8, 144.6, 169.4.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –40.68 (s, CF_2Br).

ESI-MS: *m*/*z* calcd for $C_{17}H_{14}BrF_2NO_4$ + Na [M^+ + Na]: 435.9966; found: 435.9961.

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