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Fluorinated Nitrostyrenes

Diels-Alder Reaction of β-Fluoro-β-nitrostyrenes. Synthesis of Mono-fluorinated Six-Membered Derivatives

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Abstract: The Diels-Alder reaction of β-fluoro-β nitrostyrenes with some linear dienes was investigated. A number of mono-fluorinated [4+2]-cycloadducts was prepared in up to 90 % yield. The kinetics of [4+2]-cycloaddition to 2,3-dimethyl-1,3-butadiene was studied in detail to reveal substituent effect and activation parameters of the reaction. It was demonstrated that base-induced elimination of nitrous acid followed by oxidative aromatization can be used for the preparation of mono-fluorinated biphenyls in up to 92 % isolated yield.

Introduction

Organofluorine compounds play an exceptionally important role in the development of new drugs and design of materials with unique properties. Intensive research in organofluorine chemistry is still a key trend of modern organic synthesis, despite more than 150-year history of this area. About one-fourth of currently manufactured agrochemical and pharmaceutical products contains at least one fluorine atom and their number tends to persistently rise. Indeed, only about 20 % of these products appeared on the market in the first decade of the 21st century.[1] One of the key problems in synthetic and medical chemistry is the design of structures with a strictly prescribed position of a fluorine. Incorporation of a fluorine into the molecule can positively modulate a number of important pharmacokinetic and physicochemical properties of the drug, such as lipophilicity, electrophilicity, conformation, pK_a, metabolic and chemical stability, membrane permeability and binding affinity to a target protein.[2] Recently, significant advance on the direct fluorination has been made due to the development of novel fluorinating reagents and catalytic systems.[3] However, the application of such the protocols are challenging and often limited.[4] The use of fluorinated building blocks is a very convenient approach and in many cases indispensable alternative to direct approaches.[5,6]

In this regard, Diels–Alder reaction is a powerful tool which has found wide application for assembling variety of fluorinated carbo- and heterocycles using either dienes[7–9] or dienophiles[10–13] as fluorine-containing building blocks[5,6] (Figure 1) Thus, the development of new protocols to relevant fluorinated molecules based on application of novel versatile fluorine-containing building blocks is of exceptional significance.

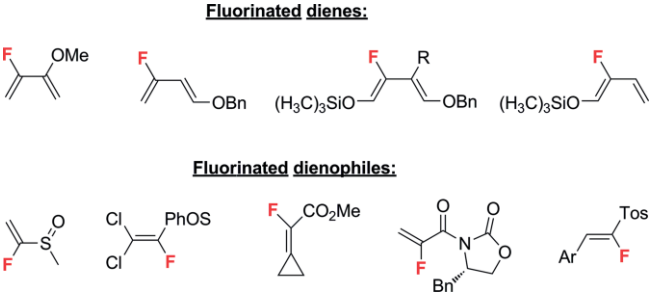

Figure 1. Selected examples of monofluorinated building blocks in Diels-Alder reaction.

Recently, we have developed the efficient stereoselective synthesis of β-fluoro-β-nitrostyrenes[14,15] and demonstrated utility of these new building blocks for the synthesis of numerous fluorinated compounds.[16] We proposed that due to electron deficient nature of nitrostyrenes these building blocks could be efficient monofluorinated dienophiles. This study is devoted to investigation of their reaction with some linear dienes to form cycloadducts **2** as well as subsequent aromatization of **2** into the corresponding mono-fluorinated biphenyls **3**.

RESULTS AND DISCUSSION

First, a set of β-fluoro-β-nitrostyrenes **1** bearing different substituents in benzene ring was prepared[14,15] to estimate the reactivity of these fluorinated building blocks in [4+2]-cycloaddition. Having in hand the set of substrates, the Diels-Alder reaction of β-fluoro-β-nitrostyrenes **1** with 2,3-dimethyl-1,3-butadiene was investigated. The reactions were conducted in screw-top vials in *o*-xylene media at 130 °C using 5-fold excess

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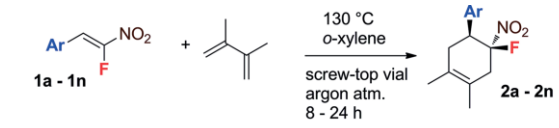
of 2,3-dimethyl-1,3-butadiene (Scheme 1). It was found that the reactions proceeded highly efficiently under these conditions to give the target cycloadducts **2** in high isolated yield (75–90 %). Moreover, the reactions can be easily scaled-up to gram amount (Scheme 1; **2h**). All the structures were elucidated by NMR and elemental analysis.



2a Ar = 4-$CH_3OC_6H_5$ (85 %)
2b Ar = 4-*t*-BuC_6H_5 (80 %)
2c Ar = 4-$CH_3C_6H_5$ (80 %)
2d Ar = C_6H_5 (80 %)
2e Ar = 4-FC_6H_5 (75 %)
2f Ar = 4-ClC_6H_5 (85 %)
2g Ar = 4-BrC_6H_5 (90 %)
2h Ar = 4-$MeO_2CC_6H_5$ (78 %) (90 %)[b]
2i Ar = 4-$CF_3C_6H_5$ (87 %)[a]
2j Ar = 2,4-$Cl_2C_6H_4$ (85 %)
2k Ar = 2-$NO_2C_6H_5$ (87 %)[a]
2l Ar = 3-$NO_2C_6H_5$ (80 %)[a]
2m Ar = 4-CNC_6H_5 (85 %)[a]
2n Ar = 4-$NO_2C_6H_5$ (73 %) (75 %)[c]

Scheme 1. Scope of nitrostyrenes in the reactions with 2,3-dimethyl-1,3-butadiene; (nitrostyrene **1** = 0.5 mmol; (a) - 1.0 mmol; (b) - 2.5 mmol; (c) - 5.0 mmol).

Additionally, we decided to have a deep insight on the reactivity of β-fluoro-β-nitrostyrenes **1** in [4+2]-cycloaddition reactions. Up to date there are very few works devoted to kinetic studies of nitrostyrenes in Diels-Alder reactions.[17,18] In this context, we aimed at detail study of kinetics of β-fluoro-β-nitrostyrenes in [4+2]-cycloaddition on the example of symmetric 2,3-dimethyl-1,3-butadiene. To our best knowledge such the multilateral investigations on the reactivity and application of ?-deficient β-fluoro-β-nitrostyrenes in [4+2]-cycloaddition are unprecedented.

All the kinetic runs were performed using *ca* 35 molar excess of 2,3-dimethyl-1,3-butadiene in o-xylene (1:1) to provide pseudo-first order conditions. Conversions (*F*) of **1** were measured by ^{1}H NMR analysis. First, the kinetic curves were obtained for the reactions of 2,3-dimethyl-1,3-butadiene with differently substituted in the benzene ring nitrostyrenes **1a – 1n** at 130 °C.

The pseudo-first order rate constants *k** were obtained with good correlation by plotting the experimental values of ln (C_0/*C*) vs. time (Table 1). The overall second-order rate constant *k* were calculated from *k** and initial concentration of diene (Table 1).

It was found that the reaction rate significantly depends on substituents in the benzene ring of nitrostyrenes **2**. We decided to study a correlation with the Hammett constants for these substituents. The effect of a substituent on the reaction rate was estimated first by plotting log k against the Hammett constants σ_p for *p*-substituent (Figure 2). A very good correlation of the plot was obtained for a series of *p*-substituted nitrostyrenes **1** according to the Hammet Equation (Equation (1)):

$$\log k = 1.00\sigma_p - 4.84 (R = 0.984) \quad (1)$$

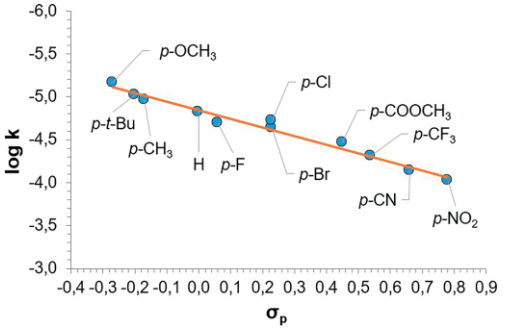


Figure 2. Plot of log k vs. Hammet constants (σ_p).

Another parameter frequently used for estimation of reactivity is a global electrophilicity index (ω).[20] In contrast to the Hammet approach it gives reliable predictions not only for para- or meta-mono-substituted derivatives, but also for both ortho-mono-substituted and multi-substituted derivatives.[21] Ground-state geometries of nitrostyrenes **1** were optimized using DFT B3LYP/6-31G* level of theory. The values of ω were evaluated from HOMO and LUMO energies for nitrostyrenes **1a-1n** (Figure 3, Equation (2)):[22]

$$\omega = \mu^2/2\eta = 1/8\ (E_{HOMO} + E_{LUMO})2/(E_{LUMO} - E_{HOMO}) \quad (2)$$

Next, the similar linear relationship was obtained between log k and ω. However, the correlation in this case was slightly worse (Figure 4).

Table 1. Kinetic parameters for the reactions of **1** with 2,3-dimethyl-1,3-butadiene at 130 °C.

Entry	Substrate **1**	Substituent R	***k****, × 10^5 s^{-1}	***k***, × 10^5 L/mol·s	$\mathbf{R_{corr}}$	**σ**[19]	ω, **eV**
1	**1a**	4-CH_3O	3.03	0.69	0.996	–0.27	2.66
2	**1b**	4-*t*Bu	4.16	0.94	>0.999	–0.20	2.76
3	**1c**	4-CH_3	4.80	1.09	0.999	–0.17	2.78
4	**1d**	H	6.66	1.51	0.997	0.00	2.87
5	**1e**	4-F	8.95	2.03	0.999	0.06	2.94
6	**1f**	4-Cl	8.47	1.92	0.998	0.23	3.10
7	**1g**	4-Br	10.31	2.33	>0.999	0.23	3.11
8	**1h**	4-CO_2Me	10.04	3.40	0.994	0.45	3.21
9	**1i**	4-CF_3	21.48	4.86	0.998	0.54	3.25
10	**1j**	2,4-Cl_2	20.92	4.73	0.998	–	3.27
11	**1k**	2-NO_2	21.90	4.95	0.999	–	3.41
12	**1l**	3-NO_2	23.11	5.23	0.997	0.71	3.43
13	**1m**	4-CN	32.03	7.25	0.998	0.66	3.56
14	**1n**	4-NO_2	42.20	9.55	0.999	0.78	3.82

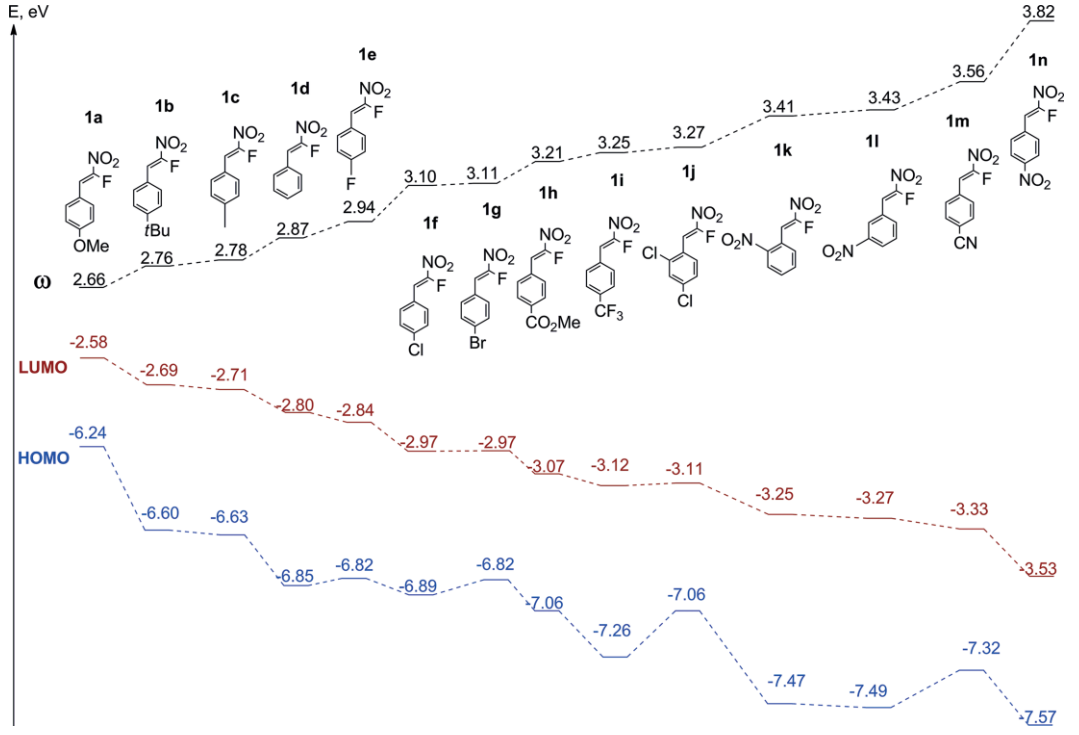


Figure 3. FMO energies and global electrophilicity indexes (ω) of β-fluoro-β-nitrostyrenes **1a – 1n**.

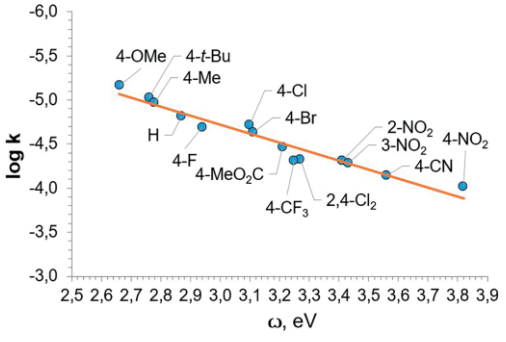


Figure 4. Plot of log k vs. global electrophilicity indexes (ω).

The relationships (Equation (1); Equation (3)) suggest a similar structure of the transition state involved in all the reactions studied. Indeed, the transition states have slightly polar character as indicated by the value of the reaction constant (ρ = 1.00). Moreover, positive value of ρ indicates that the reaction is favored by withdrawal of electron pairs from the reaction site.[23] Thus, the charge transfer with transition state takes place from the diene substructure towards the nitrostyrene substructure that is in full accordance with the theoretical prediction.

$$\log k = 1.02\omega - 7.78 \quad (R = 0.971) \qquad (3)$$

We also estimated the effect of position of nitro-group in the benzene ring (Figure 5). The experimental kinetic data obtained for the reaction of 2,3-dimethyl-1,3-butadiene with nitrostyrenes **1k**, **1l**, **1n** at 130 °C showed that the reaction rate increased for a following series: o-NO_2 < m-NO_2 < p-NO_2. Most probably the least reactivity of *o*-substituted nitrostyrene **1k** is related to the steric effect caused by the close position of nitro-group to the reaction site. Noteworthy, the high correlation between log k and ω (Figure 5) demonstrates that the experimental data is in full accordance with the theoretical DFT calculations.

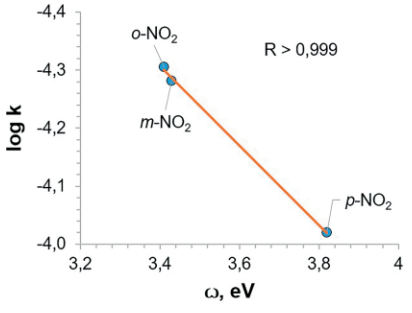


Figure 5. Effect of position nitro-group in benzene ring of nitrostyrenes **1**.

After, the relationship between the global electrophilicity (ω) and the Hammett constants (both σ_p and σ_m) was studied (Figure 6).[24] The plot obtained confirms the existence of a good linear correlation between both variable parameters from a strong electron-donating OCH_3 to a strong electron-withdrawing NO_2-group for a series of nitrostyrenes **1** (Equation (4)):

$$\omega = 0.91\ \sigma + 2.90 \quad (R = 0.964) \qquad (4)$$

Next, the substituent effect at the double bond was estimated. The kinetics studies of reactions of nitrostyrenes bearing H, F, Cl and Me at the β-carbon with 2,3-dimethyl-1,3-butadiene were carried out at 130 °C (Scheme 2).

The experimental data showed that β-unsubstituted nitrostyrene **1a-H** proved to be the most reactive one instead of β-fluorinated **1a** expected according to DFT calculations (Table 2; Figure 7). Besides, the replacement of H with CH_3-group caused

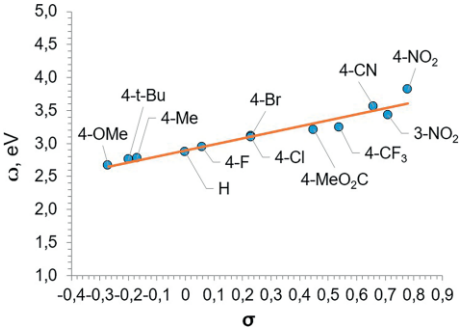
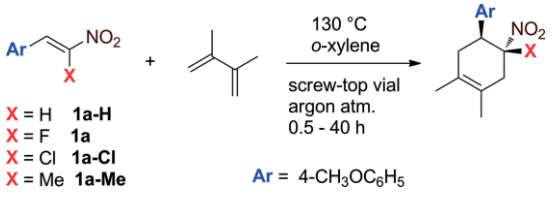


Figure 6. Plot of Hammet constants (σ) vs. global electrophilicity (ω).



Scheme 2. Kinetic study of substituent effect at β-carbon.

up to 22-fold decrease of the rate constant value (Table 2). It is obvious that this cannot be explained only by electronic effect of substituents. Indeed, a very low correlation between log k and ω was obtained. However, the noticeably higher correlation

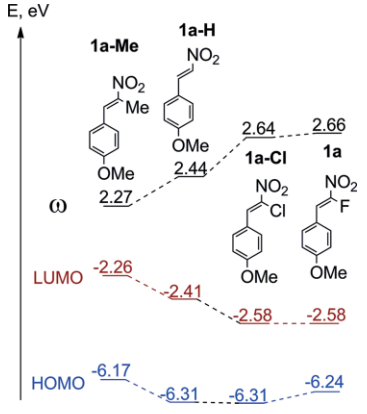


Figure 7. FMO energies and global electrophilicity indexes (ω) of β-nitrostyrenes **1a-H**, **1a**, **1a-Cl**, **1a-Me**.

was obtained for the plot of log k vs. Tafft-Kutter-Harsh steric constants ($\hat{E}s$) (Equation (5); Figure 8). The latter are linear functions of average van der Waals radii ($\bar{R}_{vdw}$) and were calculated as defined by Equation (6).[25]

$$\log k = 0.86\ \hat{E}s - 5.80 (R = 0.945) \quad (5)$$

$$\hat{E}_s = 3.484–1.839\ \bar{R}_{vdw} \quad (6)$$

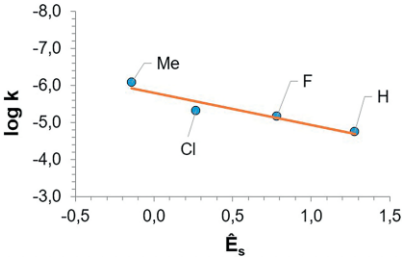


Figure 8. Plot of log k vs. $\hat{E}_s$.

This data confirms that in case of substituent at the terminal carbon the reactivity is mainly influenced by steric hindrance of the reaction site.

Finally, activation parameters for the reaction of the most reactive *p*-NO_2-substituted substrate **1n** were estimated. The kinetic studies were conducted in the temperature range of 70–130 °C. The calculated rate constants are presented in Table 3. The data obtained were plotted in Arrhenius coordinates (ln k vs. 1/T) as well as in Eyring coordinates (ln (k/T) vs. 1/T). The regression analysis gave the following linear relationships (Equation (7), Equation (8)):

$$\ln k = 10.16–7886/T (R = 0.990) \quad (7)$$

$$\ln (k/T) = 3.19–7514.8/T (R = 0.989) \quad (8)$$

The activation parameters were estimated by both Arrhenius equation (Equation (9)) and Eyring equation[27] (Equation (10)).

$$\ln k = \ln A - E_A/RT \quad (9)$$

$$\ln (k/T) = \ln (k_b/\hbar) + \Delta S^{\#}/R - \Delta H^{\#}/RT \quad (10)$$

The values obtained (Table 3) were found to be typical for concerted [4+2]-cycloaddition reactions.[18]

Table 2. Kinetic parameters for the reactions of 4-MeO-nitrostyrenes with 2,3-dimethyl-1,3-butadiene.

Entry	Substituent X	k^* × 10^6 s^{-1}	k × 10^6 L/mol·s	R_{corr}	R_{vdw},[26] Å	$\hat{E}_s$	ω, eV
1	H	78.27	17.71	0.999	1.20	1.28	2.44
2	F	30.27	6.85	0.996	1.47	0.78	2.66
3	Cl	21.02	4.76	0.999	1.75	0.27	2.64
4	Me	3.61	0.82	0.999	1.93[a]	–0.14	2.27

[a] Average between max (2.23) and min (1.715).

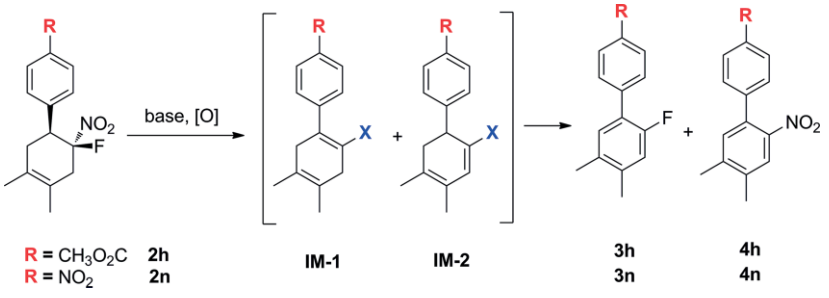
Table 3. Kinetic and thermodynamic data of the reaction **1h** with 1,3-dimethylbutadiene.

Entry	T, °C	k^* × 10^5 s^{-1}	k × 10^5 L/mol·s	R_{corr}	E_A, kJ/mol	$\Delta H^{\#}$, kJ/mol	$\Delta S^{\#}$, J/mol·K
1	70	1.25	0.28	0.998	65.53	62.45	–170.96
2	90	3.79	0.86	0.998			
3	110	9.45	2.14	>0.999			
4	130	42.20	9.55	0.999			

Next, we decided to study elimination of nitrous acid under basic conditions. We expected that a family of highly attractive monofluorinated biaryls could be prepared by this approach. Biphenyl is a key structural motif in a wide range of pharmacological active compounds. Indeed, the biaryl structure is found in 4.3 % of all known drugs which cover all therapeutic areas. Moreover, biaryl groups can be useful templates for the discovery and design of therapeutics with high affinity and specificity for a broad range of protein targets.[28] The proposed sequence included two steps. After treatment with a base we expected the formation of the corresponding cyclohexadienes. However, due to potential low stability of these intermediate products, we decided to perform aromatization in the presence of air to elaborate direct synthesis of the corresponding biphenyls.[29] In principle, competitive elimination of either HNO_2 or HF can be expected leading to the formation of either fluorine-substituted or nitro-substituted biphenyls (Scheme 3).

We performed some optimization of the reaction conditions for cycloadduct **2n** as a model compound using various bases (Table 4, entries 1–7). The reaction was performed in acetonitrile at 60 °C in the presence of atmospheric air as an oxidant. The absence of solvent as well as the further increase of temperature led to the formation of undesirable and unidentified side-products in the model reaction. When the reaction was performed in the presence of weak inorganic bases, only trace amount of biphenyl **3n** was detected by ^{19}F NMR (Table 4, entries 1–2). Low yields of the desired product **3n** were observed when excess of cesium fluoride or *t*BuOK were used (Table 4, entries 3–4). However, the application of low nucleophilic organic bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) demonstrated very good effectiveness. The corresponding mono fluorinated biaryl **4n** was isolated in up to 82 % yield (Table 4, entries 5–7). Among the base tested, DBU was selected as the most effective base. Moreover, the effectiveness of the process was noticeably enhanced when the reaction was conducted under pressure of air (Table 4, cf. entries 7, 10 with 8, 11). It should be emphasized that in all cases the transformation of cycloadduct **2n** into **3n** occurred selectively; no formation of product **4n** derived from the elimination of HF was observed. However, when cycloadduct **2h** bearing *p*-methoxycarbonyl group was subjected to the aromatization, both products **3h** and **4h** were formed in 73 and 8 % yield respectively (Table 4, entry 11). The change of the solvent media did not affect the selectivity, but reduced the product yield (Table 4, entries 12–13). Meanwhile, the use of MnO_2 as an oxidant was as effective as compressed air was. (Table 4, entries 9,13).

Having the optimized conditions in hand, the reaction was performed with a set of cycloadducts **2** (Scheme 4). First, nitrostyrenes having strong electron-withdrawing group **(**EWG) substituents were tested (Scheme 4). In all cases only two products **3** and **4** were isolated. These results demonstrate that the cyclohexadiene intermediates are prone to oxidative aromatization. To our delight, the elimination of HNO_2 proceeds predominantly. The corresponding monofluorinated biphenyls **3** were

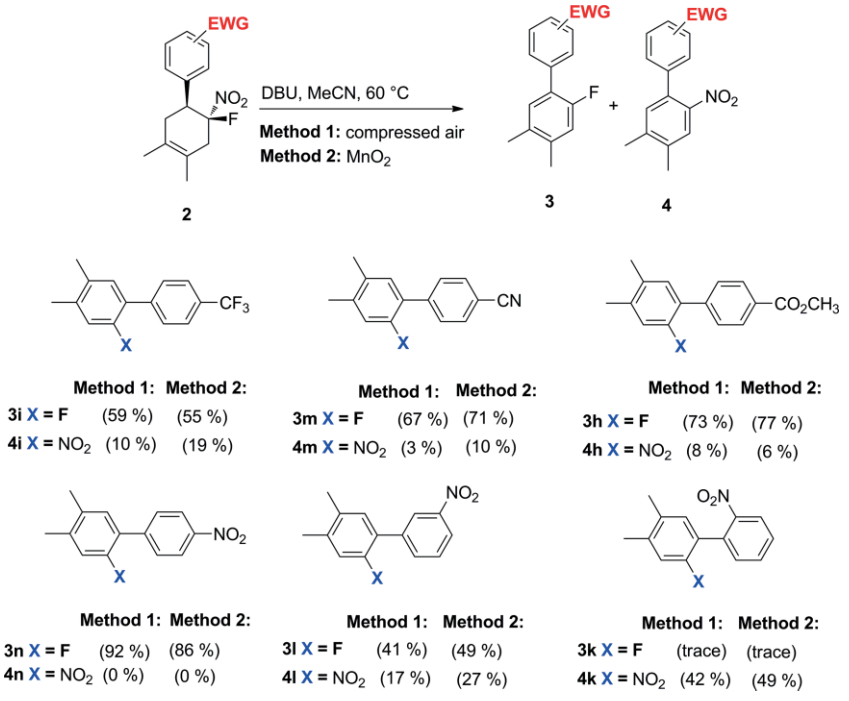


Scheme 3. Elimination-aromatization of cycloadducts **2**.

Table 4. Optimization of elimination-aromatization sequence.[a]

Entry	Substrate	base	oxidant	Solvent	Yield **3**, %	Yield **4**, %
1	**2n**	K_2CO_3 (10 equiv.)	atm. air	MeCN	trace	0
2	**2n**	KF (10 equiv.)	atm. air	MeCN	trace	0
3	**2n**	CsF (10 equiv.)	atm. air	MeCN	16	0
4	**2n**	*t*BuOK (5 equiv.)	atm. air	MeCN	14	0
5	**2n**	DBN (4 equiv.)	atm. air	MeCN	76	0
6	**2n**	TBD (4 equiv.)	atm. air	MeCN	80	0
7	**2n**	DBU (4 equiv.)	atm. air	MeCN	82	0
8	**2n**	DBU (4 equiv.)	air 1.5 bar	MeCN	**92**	**0**
9	**2n**	DBU (4 equiv.)	MnO_2 (5 equiv.)	MeCN	**86**	**0**
10	**2h**	DBU (6 equiv.)	atm. air	MeCN	50	trace
11	**2h**	DBU (6 equiv.)	air 1.5 bar	MeCN	**73**	**8**
12	**2h**	DBU (6 equiv.)	air 1.5 bar	EtOAc	68	8
13	**2h**	DBU (6 equiv.)	air 1.5 bar	THF	42	trace
14	**2h**	DBU (6 equiv.)	MnO_2 (5 equiv.)	MeCN	**77**	**6**

[a] Reaction conditions: 60 °C; concentration **2** = 0.4 M; 18–24 h.



Scheme 4. Scope of strong EWG-substituted cycloadducts **2**.

isolated in up to 92 % yield, whereas the nitro-containing derivatives **4** (elimination of HF) were isolated as minor products. Additionally, we investigated the effect of position of the nitro-group on the reaction selectivity. When the nitro-group is posed at *meta*-position, the yield of the target **3l** dropped to 41–49 %, whereas the portion of **4l** rose to 17–27 %. To our surprise, the elimination of adduct **2k** with the nitro-group at *ortho*-position led to the selective formation of non-fluorinated biphenyl **4k** in 49 % yield.

Further, the elimination for cycloadducts **2** bearing either no EWG (**2b**–**2d**) or weak EWG (**2e**–**2j**) was studied (Table 5). It was found that in this case the reaction is much more complicated. Both the chemoselectivity and yields of monofluorinated biphenyls **3** were significantly lower. In contrast, the elimination of HF intensified to give nitro-substituted biphenyls **4** in 16–41 % yield.

Table 5. Scope of cycloadducts **2** with no or weak EWG.[a]

Entry	Substrate	Ar	Selectivity, % IM-1	IM-2	3	4
1	**2b**	4-*t*-BuC_6H_5	15	2	4	27
2[b]	**2c**	4-MeC_6H_5	23	2	3	41
3	**2d**	C_6H_5	12	trace	2	16
4	**2e**	4-FC_6H_5	5	trace	1	30
5	**2f**	4-ClC_6H_5	6.5	1	13.5	38
6	**2g**	4-BrC_6H_5	5	1	19	32
7	**2j**	2,4-$Cl_2C_6H_4$	18	trace	3	26

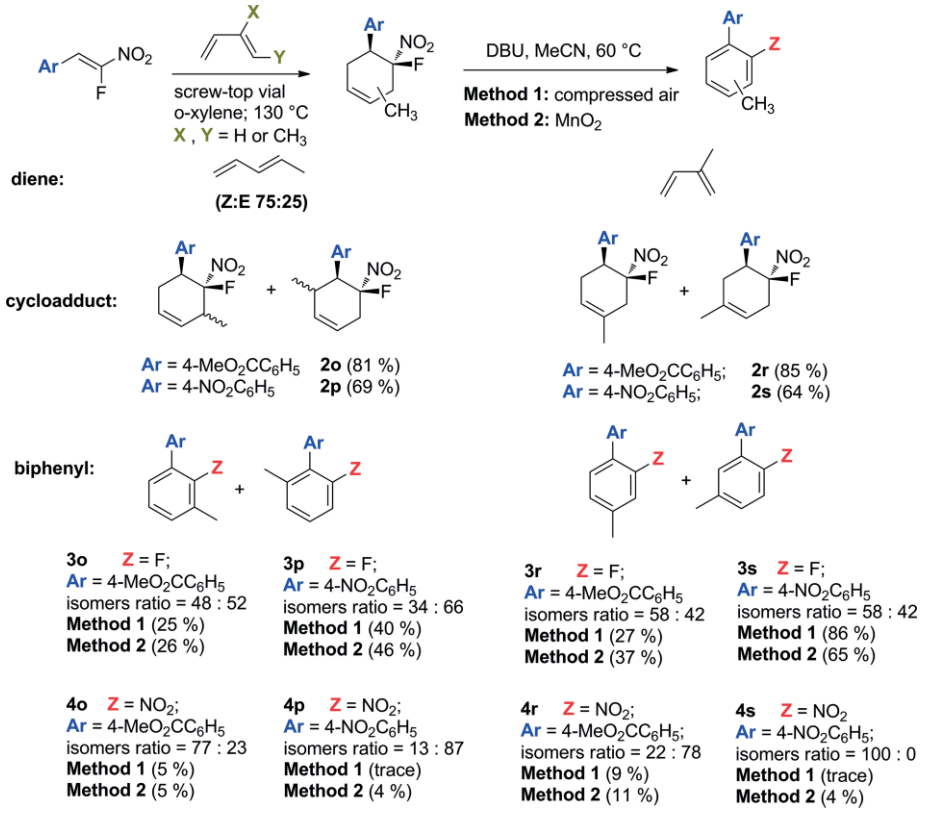
[a] 60 °C, compressed air, DBU (8 mol. equiv.), 18–24 h. [b] 80 °C, MnO_2 (5 mol. equiv.), DBU (8 mol. equiv.), 18 h.

Moreover, it was observed that the fluorine-containing cyclohexadiene intermediates with no or weak EWG are difficult to oxidize by both oxygen and MnO_2 in acetonitrile even at 80 °C. However, the treatment of the reaction mixture with MnO_2 in toluene for 5 h at 80 °C made aromatization successful to give **3j** in 15 % isolated yield. As result the formation of inseparable mixtures of fluorinated non-oxidized cyclohexadiene intermediates **IM-1**, **IM-2** and biphenyl **3** were observed. On the contrary, the formation of *ortho*-nitro biphenyls **4** proceeds cleanly to demonstrate that the presence of strong EWG is important to facilitate oxidative aromatization.

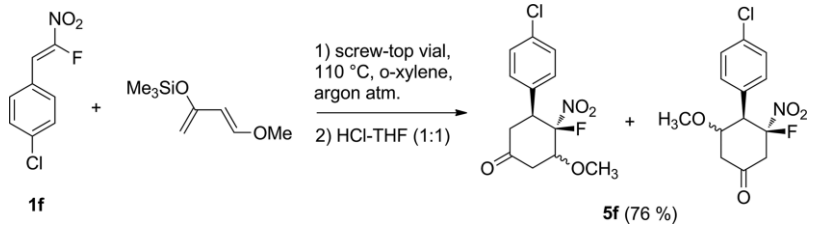
Next, the reactions of nitrostyrenes **1n, 1h** with isoprene and piperylene were studied. The corresponding cycloadducts **2** were isolated in high yield (64–85 %) confirming general character of the cycloaddition (Scheme 5). As expected, the reactions are more complex due to unsymmetrical structure of both reactants. According to analysis of NMR, the mixture of regio- and stereoisomers is formed. Nevertheless, the subsequent elimination-aromatization eventually gives the target product **3** as a mixture of two regioisomers having different position of methyl groups.

The aromatizaton of cycloadducts **2o**–**2s** demonstrated the similar pattern in terms of selectivity as that of cycloadducts **2h; 2n** did. In case of piperylene derived cycloadducts **2o** and **2p** the yields of the desired products **3o** and **3p** were in range 25–46 %; the yields of the side products **4o** and **4p** did not exceed 5 %. When isoprene based cycloadduct **2r** underwent to the aromatization process in the presence of MnO_2, 37 % of mono-fluorinated biphenyls **3r** was obtained along with 11 % of the side products **4r**. On the contrary nitro-substituted cycloadduct **2s** was selectively transformed into the target products **3s** in high yield (86 %) under compressed air.

Finally, the Diels-Alder reaction of nitrostyrene **1f** with (*E*)-1-methoxy-3-trimethylsilyloxy-buta-1,3-diene (Danishefsky's di-



Scheme 5. Preparation of cycloadducts and biphenyls based on unsymmetrical 1,3-dienes.



Scheme 6. Diels-Alder reaction of nitrostyrene **1f** with Danishefsky's diene.

ene) was studied (Scheme 6). Due to electron-rich nature of this diene the reaction was complete at 110 °C within 7.5 h. Subsequent hydrolysis of TMS-group by THF/water solution of HCl resulted in the formation of the mixture of regio- and stereoisomers of the corresponding cyclohexanones **5f** in 76 % total yield.

In summary, the Diels-Alder reaction of β-fluoro-β-nitrostyrenes with linear dienes was investigated. A series of novel monofluorinated [4+2]-cycloadducts was prepared in high yield up to 90 %. The kinetic studies of [4+2]-cycloaddition reaction of a series of nitrostyrenes with 2,3-dimethyl-1,3-butadiene were carried out considering substituent effect in the benzene ring and at the terminal β-carbon. The global electrophilicity indexes were evaluated for a wide range of nitrostyrenes **1**. The experimental data demonstrated that the substituent effect in the benzene ring was in agreement with both the Hammet equation and DFT calculations. The activation parameters of the reaction were found to be typical for concerted [4+2]-cycloaddition reactions. In addition, the elimination-aromatization sequence for the synthesis of the corresponding mono-fluorinated biphenyls was elaborated. It was found that the selectivity of the process and oxidizability of cycloadducts depends on the nature and position of substituents in the benzene ring. The adducts bearing strong electron-withdrawing groups at *para*-position can be transformed into the desired biphenyls in selective manner in up to 92 % isolated yield.

Experimental Section

All reagents were purchased from commercial sources and used without any further purification except for piperylene and isoprene. The latter were purified by distillation before use. Piperylene was composed of 75 % of *Z*- and 25 % of *E*-isomer. All solvents were dried before use by passing through a column charged with activated neutral alumina[30] or with the standard procedures. Melting points (M.p.) were measured with a Büchi B-545 melting point apparatus. NMR (^{1}H, ^{13}C and ^{19}F) spectra were obtained with Bruker AV-400 and Agilent 400-MR spectrometers using deuterated chloro-

form ($CDCl_3$). Chemical shifts for ^1H NMR spectroscopic data were referenced to internal tetramethylsilane (δ = 0.0 ppm) and the residual solvent resonance (δ = 7.26 ppm); chemical shifts for ^{13}C NMR spectroscopic data were referenced to residual solvent resonance (δ = 77.16 ppm); chemical shifts for ^{19}F NMR spectroscopic data were referenced to $PhCF_3$ (δ = –63.72 ppm). Data are reported as follows: chemical shift, integration multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, qui = quintet, sext = sextet, sept = septet, br = board, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets) and coupling constants (Hz). Starting β-fluoro-β-nitrostyrenes were prepared according to the described procedures.[14,15] Nitrostyrenes **1a**, **1c**, **1d**, **1e**, **1f**, **1h**, **1k**, **1m**, **1n**;[14] **1b**, **1g**;[31]**1i**;[32] **1j**[33] are known compounds.

1-(2-Bromo-2-fluorovinyl)-3-nitrobenzene. 3-Nitrobenzaldehyde (15.133 g, 100 mmol) was added portionwise to the solution of hydrazine hydrate (5.3 mL, 110 mmol) in ethanol (400 mL) with stirring. After completion of hydrazone formation (TLC monitoring), the reaction mixture was cooled to 0 °C in ice-water bath and CBr_3F (14.7 mL, 150 mmol) was added. Then solution of ethylene diamine (10 mL, 150 mmol) and CuCl (200 mg, 3 mmol) in ethanol (100 mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. After the reaction mixture was filtered and concentrated under vacuum. The resulting mixture was dissolved in DCM (150 mL) and poured into 5 % aqueous HCl solution (150 mL). The product was extracted with DCM, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The product was isolated as *E*/*Z*-isomers mixture (74:26) by column chromatography on silica gel using hexane/DCM (1:1) as eluent; 20.850 g (85 %); yellowish oil; *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, $^3J_{H,F}$ = 14.5 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.69–7.73 (m, 1H), 8.00–8.03 (m, 1H), 8.22 (t, *J* = 1.9 Hz, 1H) ppm; *E*-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 5.97 (d, $^3J_{H,F}$ = 32.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.56–7.60 (d, *J* = 7.8 Hz, 1H), 7.98 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.05 (t, *J* = 1.9 Hz, 1H) ppm. Analysis of the sample matched the previously reported data.[34]

(Z)-1-(2-Fluoro-2-nitrovinyl)-3-nitrobenzene (1l). $Fe(NO_3)_3{\cdot}9H_2O$ (99.20 g, 246 mmol) in dioxane (985 mL) was added into a flask with 1-(2-bromo-2-fluorovinyl)-3-nitrobenzene (20.14 g, 82 mmol). The reaction mixture was refluxed at 100 °C for 2.5 h with vigorous stirring. After completion of the reaction (TLC control), the reaction mixture was cooled to room temperature, filtered through a paper filter and concentrated under vacuum. The residue was dissolved in DCM (150 mL), poured into water (150 mL). The product was extracted with DCM, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The pure product was isolated by column chromatography on silica gel using Hex/DCM (2:1; 1:1) as elution mixture. 13.30 g (77 %); yellow solid; M.p. 95–97 °C (Hex/DCM, 1:1). Anal. calcd. for $C_8H_5FN_2O_4$: C, 45.29; H, 2.38; N, 13.21; found C, 45.13, H, 2.25, N, 13.16; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, $^3J_{H,F}$ = 25.0 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.98–8.03 (m, 1H), 8.31 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 8.48 (t, *J* = 1.8 Hz, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.5 (d, $^2J_{C,F}$ = 6.0 Hz); 125.1 (d, $^3J_{C,F}$ = 8.0 Hz), 125.7 (d, $^4J_{C,F}$ = 2.3 Hz), 129.5 (d, $^3J_{C,F}$ = 6.3 Hz), 130.6, 136.1 (d, $^4J_{C,F}$ = 7.7 Hz), 148.6, 153.1 (d, $^1J_{C,F}$ = 299.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –109.37 (d, $^3J_{H,F}$ = 25.0 Hz) ppm.

General procedure for the Diels-Alder reaction of β-fluoro-β-nitrostyrenes and dienes

In a typical experiment, β-fluoro-β-nitrostyrene **1** (0.5 mmol), *o*-xylene (0.2 mL) and diene (2.5 mmol) were successively loaded into a screw-top vial filled with argon. After the cap was screwed tightly, the reaction mixture was heated at 130 °C with vigorous stirring for appropriate time (8–24 h). After completion of the reaction (^1H NMR analysis monitoring), the excess of the diene and *o*-xylene were evaporated under vacuum. The pure product was isolated by column chromatography using mixture of Hex/DCM as eluent.

Synthesis of 2,3-dimethyl-1,3-butadiene based cycloadducts 2

(1R*,2R*)-2-Fluoro-4′-methoxy-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2a**). Eluent: Hex/DCM (2:1); 0.115 g (85 %), pale yellow solid; M.p. 102–103 °C (Hex/DCM, 2:1). Anal. calcd. for $C_{15}H_{18}FNO_3$ (%): C, 64.50; H, 6.50; N, 5.01; found C, 64.52; H, 6.48; N, 4.97. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.75 (m, 6H), 2.34 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 6.0 Hz, 1H), 2.47–2.71 (m, 2H), 3.19 (dd, $^3J_{H,F}$ = 34.9 Hz, $^2J_{H,H}$ = 18 Hz, 1H), 3.68 (ddd, $^3J_{H,F}$ = 31.5 Hz, $^3J_{H,H}$ = 12.2, 6.0 Hz, 1H), 3.77 (s, 3H), 6.79–6.85 (m, 2H), 7.19 (d, $^3J_{H,H}$ = 7.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 37.0 (d, $^3J_{C,F}$ = 3.6 Hz), 41.5 (d, $^2J_{C,F}$ = 24.3 Hz), 45.8 (d, $^2J_{C,F}$ = 19.6 Hz), 55.3, 114.1, 120.3, 121.0 (d, $^1J_{C,F}$ = 242.0 Hz), 126.0, 127.8, 129.9, 159.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –140.85 – –140.58 (m) ppm.

(1R*,2R*)-4′-(*tert*-Butyl)-2-fluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2b**). Hex/DCM (6:1); 0.122 g (80 %), colorless solid; M.p. 108–110 °C (Hex/DCM, 6:1). Anal. calcd. for $C_{18}H_{24}FNO_2$ (%): C, 70.79; H, 7.92; N, 4.59; found C, 70.81; H, 7.95; N, 4.62. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 1.73 (s, 6H), 2.37 (dd, $^2J_{H,H}$ = 17.6 Hz, $^3J_{H,H}$ = 6.0 Hz, 1H), 2.50–2.73 (m, 2H), 3.20 (dd, $^3J_{H,F}$ = 35.0 Hz, $^2J_{H,H}$ = 17.8 Hz, 1H), 3.73 (ddd, $^3J_{H,F}$ = 31.6 Hz, $^3J_{H,H}$ = 12.1, 6.0 Hz, 1H), 7.21 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 2H), 7.30–7.34 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 31.4, 34.6, 37.0 (d, $^3J_{C,F}$ = 3.4 Hz), 41.6 (d, $^2J_{C,F}$ = 24.3 Hz), 46.0 (d, $^2J_{C,F}$ = 19.5 Hz), 120.3, 120.9 (d, $^1J_{C,F}$ = 242.4 Hz), 125.7, 126.1, 128.5 (d, $^4J_{C,F}$ = 0.9 Hz), 132.7, 151.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.73 – –135.46 (m) ppm.

(1R*,2R*)-2-Fluoro-4,4′,5-trimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2c**). Eluent: Hex/DCM (3:1); 0.117 g (80 %); colorless solid; M.p. 96–98 °C (Hex/DCM, 3:1); Anal. calcd. for $C_{15}H_{18}FNO_2$ (%):C, 68.42; H, 6.89; N, 5.32; found C, 68.47; H, 6.83; N, 5.33. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70–1.76 (m, 6H), 2.32 (s, 3H), 2.37 (dd, $^2J_{H,H}$ = 17.0 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H), 2.56 (dd, $^2J_{H,H}$ = 17.6 Hz, $^3J_{H,F}$ = 17.3 Hz, 1H), 2.62–2.74 (dd, $^2J_{H,H}$ = 17.0 Hz, $^3J_{H,H}$ = 12.1 Hz, 1H), 3.21 (dd, $^3J_{H,F}$ = 35.0 Hz, $^2J_{H,H}$ = 17.6 Hz, 1H), 3.71 (ddd, $^3J_{H,F}$ = 31.5 Hz, $^3J_{H,H}$ = 12.1, 5.8 Hz, 1H), 7.12 (d, $^3J_{H,H}$ = 7.9 Hz, 2H), 7.18 (d, $^3J_{H,H}$ = 7.9 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 21.2, 37.0 (d, $^3J_{C,F}$ = 3.6 Hz), 41.5 (d, $^2J_{C,F}$ = 24.3 Hz), 46.2 (d, $^2J_{C,F}$ = 19.6 Hz), 120.3, 120.9 (d, $^1J_{C,F}$ = 242.5 Hz), 126.0, 128.7 (d, $^4J_{C,F}$ = 1.9 Hz), 129.4, 132.8, 138.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –136.84 to –136.56 (m) ppm.

(1R*,2R*)-2-Fluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2d**). Eluent: Hex/DCM (3:1); 0.099 g (80 %), colorless solid; M.p. 109–110 °C (Hex/DCM, 3:1). Anal. calcd. for $C_{14}H_{16}FNO_2$ (%): C, 67.45; H, 6.47; N, 5.62; found C, 67.38; H, 6.31; N, 5.64. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.78 (m, 6H), 2.39 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 6.0 Hz, 1H), 2.50–2.76 (m, 2H), 3.22 (dd, $^3J_{H,F}$ = 34.7 Hz, $^2J_{H,H}$ = 17.0 Hz, 1H), 3.75 (ddd, $^3J_{H,F}$ = 31.7, $^3J_{H,H}$ = 12.1, 6.0 Hz, 1H), 7.30 (s, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 37.0 (d, $^3J_{C,F}$ = 3.3 Hz), 41.5 (d, $^2J_{C,F}$ = 24.3 Hz), 46.5 (d, $^2J_{C,F}$ = 19.5 Hz), 120.3, 120.8 (d, $^1J_{C,F}$ = 242.6 Hz), 125.9, 128.3, 128.7, 128.8 (d, $^4J_{C,F}$ = 1.6 Hz), 135.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.56 (ddd, *J* = 34.7, 31.7, 16.7) ppm.

(1R*,2R*)-2,4′-Difluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2e**). Eluent: Hex/DCM (3:1); 0.102 g (75 %); colorless oil; Anal. calcd. for $C_{14}H_{15}F_2NO_2$ (%): C, 62.91; H, 5.66; N, 5.24; found C, 62.89; H, 5.65; N, 5.18. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.75 (m, 6H), 2.36 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 6.1 Hz, 1H), 2.50–2.68

(m,2H), 3.19 (dd, $^3J_{H,F}$ = 35.0 Hz, $^2J_{H,H}$ = 17.6 Hz, 1H), 3.74 (ddd, $^3J_{H,F}$ = 31.6 Hz, $^3J_{H,H}$ = 12.3, 6.1 Hz, 1H), 6.95–7.02 (m, 2H), 7.22–7.29 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 37.0 (d, $^3J_{C,F}$ = 3.2 Hz), 41.4 (d, $^2J_{C,F}$ = 24.3 Hz), 45.8 (d, $^2J_{C,F}$ = 19.6 Hz), 115.6 (d, $^2J_{C,F}$ = 21.4 Hz), 120.4, 120.7 (d, $^1J_{C,F}$ = 242.3 Hz), 125.8, 130.5 (dd, $^3J_{C,F}$ = 8.2 Hz, $^4J_{C,F}$ = 1.7 Hz), 131.7 (d, $^4J_{C,F}$ = 2.9 Hz), 162.6 (d, $^1J_{C,F}$ = 247.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –136.02 (ddd, J = 35.0, 31.6, 16.9 Hz), –114.02 to –113.92 (m) ppm.

(1R*,2R*)-4′-Chloro-2-fluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2f**). Eluent: Hex/DCM (3:1); 0.121 g (85 %), colorless solid; M.p. 77–79 °C (Hex/DCM, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.75 (m, 6H), 2.36 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 6.1 Hz, 1H), 2.46–2.67 (m, 2H), 3.18 (dd, $^3J_{H,F}$ = 35.1 Hz, $^2J_{H,H}$ = 17.6 Hz, 1H), 3.72 (ddd, $^3J_{H,F}$ = 31.1 Hz, $^3J_{H,H}$ = 12.2, 6.1 Hz, 1H), 7.21 (d, $^3J_{H,H}$ = 8.5 Hz, 2H), 7.27 (d, $^3J_{H,H}$ = 8.5 Hz, 2H) ppm. Analysis of the sample was consistent with the data reported in the literature.[14]

(1R*,2R*)-4′-Bromo-2-fluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2g**). Eluent: Hex/DCM (3:1); 0.128g (91 %), colorless solid; M.p. 93–95 °C (Hex/DCM, 3:1). Anal. calcd. for $C_{14}H_{15}BrFNO_2$ (%): C, 51.24; H, 4.61; N, 4.27; found C, 51.21; H, 4.60; N, 4.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 6H), 2.35 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 6.0 Hz, 1H), 2.49–2.67 (m, 2H), 3.17 (dd, $^3J_{H,F}$ = 35.0 Hz, $^2J_{H,H}$ = 17.9 Hz, 1H), 3.70 (ddd, $^3J_{H,F}$ = 31.0 Hz, $^3J_{H,H}$ = 12.2, 6.0 Hz, 1H), 7.15 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 0.8 Hz, 2H), 7.39–7.44 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 36.8 (d, $^3J_{C,F}$ = 3.2 Hz), 41.4 (d, $^2J_{C,F}$ = 24.2 Hz), 46.0 (d, $^2J_{C,F}$ = 19.6 Hz), 120.4, 120.5 (d, $^1J_{C,F}$ = 242.7 Hz), 122.4, 125.7, 130.5 (d, $^4J_{C,F}$ = 1.6 Hz), 131.9, 134.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.91 to –135.61 (m) ppm.

Methyl (1R*,2R*)-2′-fluoro-4′,5′-dimethyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carboxylate (**2h**). Eluent: Hex/DCM (2:1); 0.118 g (78 %) obtained from 0.5 mmol of nitrostyrene **1h**; 0.615 g (90 %) obtained from 2.5 mmol of nitrostyrene **1h**; colorless solid; M.p. 81–83 °C (Hex/DCM, 2:1); HRMS (ESI): calcd. for $C_{16}H_{19}FNO_4$ $[M + H]^+$ = 308.1298, found 308.1292; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 6H), 2.35 (dd, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 6.0 Hz, 1H), 2.47–2.70 (m, 2H), 3.16 (dd, $^3J_{H,F}$ = 35.1 Hz, $^2J_{H,H}$ = 17.6 Hz, 1H), 3.78 (ddd, $^3J_{H,F}$ = 30.9 Hz, $^3J_{H,H}$ = 12.2, 6.0 Hz, 1H), 3.87 (s, 3H), 7.34 (d, $^3J_{H,H}$ = 7.5 Hz, 2H), 7.94 (d, $^3J_{H,H}$ = 8.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 18.4, 36.7 (d, $^3J_{C,F}$ = 3.5 Hz), 41.4 (d, $^2J_{C,F}$ = 24.2 Hz), 46.4 (d, $^2J_{C,F}$ = 19.4 Hz), 120.4 (d, $^1J_{C,F}$ = 243.1 Hz), 120.4 (d, $^3J_{C,F}$ = 0.5 Hz), 125.6, 128.9 (d, $^4J_{C,F}$ = 2.3 Hz), 129.9, 130.0, 141.0 (d, $^3J_{C,F}$ = 1.0 Hz), 166.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.67 to –135.32 (m) ppm.

(1R*,2R*)-2-Fluoro-4,5-dimethyl-2-nitro-4′-(trifluoromethyl)-1,2,3,6-tetrahydro-1,1′-biphenyl (**2i**). Eluent: Hex/DCM (5:1); 0.278 g (87 %) obtained from 1.0 mmol of nitrostyrene **1i**; colorless solid; M.p. 68–69 °C (Hex/DCM, 5:1). Anal. calcd. for $C_{15}H_{15}F_4NO_2$ (%): C, 56.78; H, 4.77; N, 4.41; found C, 56.76; H, 4.72; N, 4.41. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (s, 6H), 2.38 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H), 2.51–2.74 (m, 2H), 3.20 (dd, $^3J_{H,F}$ = 35.1 Hz, $^2J_{H,H}$ = 17.7 Hz, 1H), 3.84 (ddd, $^3J_{H,F}$ = 30.9 Hz, $^3J_{H,H}$ = 12.2, 6.1 Hz, 1H), 7.43 (d, $^3J_{H,H}$ = 8.1 Hz, 2H), 7.57 (d, $^3J_{H,H}$ = 8.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 18.4, 36.8 (d, $^3J_{C,F}$ = 3.4 Hz), 41.4 (d, $^2J_{C,F}$ = 24.2 Hz), 46.3 (d, $^2J_{C,F}$ = 19.6 Hz), 120.4 (d, $^1J_{C,F}$ = 243.0 Hz), 120.5, 124.1 (q, $^1J_{C,F}$ = 272.1 Hz), 125.6, 125.7 (q, $^3J_{C,F}$ = 3.8 Hz), 129.3 (d, $^4J_{C,F}$ = 2.3 Hz), 130.4 (q, $^2J_{C,F}$ = 32.5 Hz), 140.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –136.51 (ddd, J = 35.1, 31.0, 17.0 Hz, 1F), –63.75 (s, 3F) ppm.

(1R*,2R*)-2′,4′-Dichloro-2-fluoro-4,5-dimethyl-2-nitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2j**). Eluent: Hex/DCM (3:1); 0.137 g (85 %), colorless solid; M.p. 115–117 °C (Hex/DCM, 3:1). Anal. calcd. for $C_{14}H_{14}Cl_2FNO_2$ (%): C, 52.85; H, 4.44; N, 4.40; found C, 52.81; H, 4.27; N, 4.19. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 6H), 2.40 (d, $^3J_{H,H}$ = 9.0 Hz, 2H), 2.57 (dd, $^2J_{H,H}$ = 17.2 Hz, $^3J_{H,F}$ = 16.8 Hz, 1H), 3.19 (dd, $^3J_{H,F}$ = 35.3 Hz, $^2J_{H,H}$ = 17.2 Hz, 1H), 4.44 (dt, $^3J_{H,F}$ = 32.0 Hz, $^3J_{H,H}$ = 9.0 Hz, 1H), 7.21 (dd, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 2.2 Hz, 1H), 7.37 (d, $^4J_{H,H}$ = 2.2 Hz, 1H), 7.50 (dd, $^3J_{H,H}$ = 8.5 Hz, $^5J_{H,H}$ = 1.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 18.0, 36.5 (d, $^3J_{C,F}$ = 3.2 Hz), 40.9 (d, $^2J_{C,F}$ = 18.5 Hz), 41.4 (d, $^2J_{C,F}$ = 24.6 Hz), 120.1 (d, $^1J_{C,F}$ = 243.0 Hz), 120.6, 125.8, 127.8, 129.6 (d, $^3J_{C,F}$ = 7.5 Hz), 129.8, 133.1 (d, $^4J_{C,F}$ = 1.9 Hz), 134.4, 135.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –134.64 (ddd, J = 35.3, 32.0, 16.8 Hz) ppm.

(1R*,2R*)-2-Fluoro-4,5-dimethyl-2,2′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2k**). Eluent: Hex/DCM (2:1); 0.257 g (87 %) obtained from 1.0 mmol of nitrostyrene **1k**; pale orange solid; M.p. 149–150 °C (Hex/DCM = 2:1); Anal. calcd. for $C_{14}H_{15}FN_2O_4$ (%): C, 57.14; H, 5.14; N, 9.52; found C, 57.22; H, 5.20; N, 9.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 3H), 1.73 (s, 3H), 2.48–2.72 (m, 3H), 3.05 (dd, $^3J_{H,F}$ = 36.5 Hz, $^2J_{H,H}$ = 17.2 Hz, 1H), 4.49 (ddd, $^3J_{H,F}$ = 31.0 Hz, $^3J_{H,H}$ = 11.6, 6.4 Hz, 1H), 7.37–7.43 (m, 1H), 7.51–7.57 (m, 1H), 7.70–7.77 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 37.2 (d, $^3J_{C,F}$ = 3.4 Hz), 40.1 (d, $^2J_{C,F}$ = 17.9 Hz), 42.0 (d, $^2J_{C,F}$ = 24.7 Hz), 120.0 (d, $^1J_{C,F}$ = 244.0 Hz), 120.4, 124.7, 125.9, 128.9, 129.3 (d, $^3J_{C,F}$ = 7.7 Hz), 130.6 (d, $^4J_{C,F}$ = 2.2 Hz), 133.0, 150.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.11 (ddd, J = 35.8, 31.0, 16.5 Hz) ppm.

(1R*,2R*)-2-Fluoro-4,5-dimethyl-2,3′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2l**). Eluent: Hex/DCM (5:1); 0.236 g (80 %); pale yellow solid; M.p. 126–128 °C (Hex/DCM=, 5:1); Anal. calcd. for $C_{14}H_{15}FN_2O_4$ (%): C, 57.14; H, 5.14; N, 9.52; found C, 57.10; H, 5.12; N, 9.47. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 6H), 2.41 (dd, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H), 2.51–2.74 (m, 2H), 3.18 (dd, $^3J_{H,F}$ = 35.4 Hz, $^2J_{H,H}$ = 17.6 Hz, 1H), 3.88 (ddd, $^3J_{H,F}$ = 30.5 Hz, $^3J_{H,H}$ = 12.2, 6.2 Hz, 1H), 7.47 (t, $^3J_{H,H}$ = 7.9 Hz, 1H), 7.62 (d, $^3J_{H,H}$ = 7.6 Hz, 1H), 8.09–8.20 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 18.4, 36.6 (d, $^3J_{C,F}$ = 3.3 Hz), 41.2 (d, $^2J_{C,F}$ = 24.0 Hz), 46.1 (d, $^2J_{C,F}$ = 19.7 Hz), 120.2 (d, $^1J_{C,F}$ = 243.0 Hz), 120.5, 123.3, 123.8 (d, $^4J_{C,F}$ = 2.3 Hz), 125.4, 129.8, 135.1 (d, $^4J_{C,F}$ = 2.2 Hz), 138.0, 148.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –136.59 (ddd, J = 35.1, 30.5, 17.1 Hz) ppm.

(1R*,2R*)-2′-Fluoro-4′,5′-dimethyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carbonitrile (**2m**). Eluent: Hex/DCM (1:1); 0.232 g (85 %) obtained from 1.0 mmol of nitrostyrene **1m**; colorless solid; M.p. 117–118 °C (Hex/DCM, 1:1). Anal. calcd. for $C_{15}H_{15}FN_2O_2$ (%): C, 65.88; H, 5.51; N, 10.21; found C, 65.76; H, 5.55; N 10.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 6H), 2.35 (dd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H), 2.48–2.69 (m, 2H), 3.16 (dd, $^3J_{H,F}$ = 35.1 Hz, $^2J_{H,H}$ = 17.8 Hz, 1H), 3.80 (ddd, $^3J_{H,F}$ = 30.8 Hz, $^3J_{H,H}$ = 12.1, 6.1 Hz, 1H), 7.39 (d, $^3J_{H,H}$ = 7.8 Hz, 2H), 7.53–7.61 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 18.4, 36.5 (d, $^3J_{C,F}$ = 3.4 Hz), 41.2 (d, $^2J_{C,F}$ = 24.0 Hz), 46.4 (d, $^2J_{C,F}$ = 19.4 Hz), 112.2, 118.4, 120.1 (d, $^1J_{C,F}$ = 243.2 Hz), 120.5, 125.3, 129.6 (d, $^4J_{C,F}$ = 2.3 Hz), 132.4, 141.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –136.47 (ddd, J = 35.1, 30.8, 17.0 Hz) ppm.

(1R*,2R*)-2-Fluoro-4,5-dimethyl-2,4′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl (**2n**). Eluent: Hex/DCM (2:1); 0.107 g (73 %) obtained from 0.5 mmol of nitrostyrene **1n**; 1.120 g (75 %) obtained from 5.0 mmol of nitrostyrene **1n**; colorless solid; M.p. 115–116 °C (Hex/DCM, 2:1). Anal. calcd. for $C_{14}H_{15}FN_2O_4$ (%): C, 57.14; H, 5.14; N, 9.52; found C, 57.04; H, 5.02; N, 9.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 6H), 2.38 (dd, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 5.9 Hz, 1H), 2.51–2.70 (m, 2H), 3.17 (dd, $^3J_{H,F}$ = 35.2 Hz, $^2J_{H,H}$ = 17.7 Hz, 1H), 3.87 (ddd, $^3J_{H,F}$ = 30.5 Hz, $^3J_{H,H}$ = 12.2, 5.9 Hz, 1H) 7.46 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 8.13 (dd, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,H}$ = 1.9 Hz, 2H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 18.4, 18.5, 36.7 (d, $^3J_{C,F}$ = 2.8 Hz), 41.3 (d, $^2J_{C,F}$ = 24.1 Hz), 46.3 (d, $^2J_{C,F}$ = 19.6 Hz), 120.1 (d, $^1J_{C,F}$ = 243.5 Hz), 120.6, 123.8, 125.4, 129.9 (d, $^4J_{C,F}$ = 2.1 Hz), 143.4, 147.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.40 (ddd, *J* = 35.2, 30.5, 17.1 Hz) ppm.

Synthesis of piperyline based cycloadducts 2

(1′S*,2′S*)-Methyl 2′-Fluoro-3′-methyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carboxylate and (1′S*,2′S*)-Methyl 2′-Fluoro-6′-methyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carboxylate (2o). Eluent: Hex/DCM (1:1), DCM; 0.124 g (81 %); colorless oil. Anal. calcd. for $C_{15}H_{16}FNO_4$ (%): C, 61.43; H, 5.50; N, 4.78; found C, 61.72; H, 5.50; N, 4.72. Isomers ratio 35:11:7:29:8:10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–1.27 (m, 6H), 1.45–1.83 – (m, 2H), 2.44–2.89 (m, 4H), 3.02–3.45 (m, 2H), 3.86–3.91 (m, 6H), 5.25–5.96 (m, 4H), 7.15–7.46 (m, 4H), 7.92–8.04 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0 (d, $^3J_{C,F}$ = 7.1 Hz), 15.9 (d, $^3J_{C,F}$ = 4.3 Hz), 17.5 (d, $^3J_{C,F}$ = 7.4 Hz), 17.9 (d, $^3J_{C,F}$ = 4.8 Hz), 19.1, 31.0 (d, $^3J_{C,F}$ = 3.6 Hz), 32.6 (d, $^3J_{C,F}$ = 4.2 Hz), 35.1 (d, $^3J_{C,F}$ = 2.8 Hz), 35.8, 36.1 (d, $^3J_{C,F}$ = 3.7 Hz), 39.4 (d, $^2J_{C,F}$ = 22.2 Hz), 39.5 (d, $^2J_{C,F}$ = 24.6 Hz), 41.9 (d, $^2J_{C,F}$ = 19.4 Hz), 47.1 (d, $^2J_{C,F}$ = 20.1 Hz), 49.0 (d, $^2J_{C,F}$ = 17.7 Hz), 52.2, 52.3, 53.4 (d, $^2J_{C,F}$ = 19.3 Hz), 119.2, 119.5, 119.6, 120.1 (d, $^1J_{C,F}$ = 244.6 Hz), 120.8 (d, $^1J_{C,F}$ = 246.7 Hz), 124.9, 125.3, 126.7, 127.6, 127.8, 128.0 (d, $J_{C,F}$ = 4.9 Hz), 128.5 (d, $J_{C,F}$ = 4.2 Hz), 128.9 (d, $J_{C,F}$ = 2.2 Hz), 129.1 (d, $J_{C,F}$ = 2.9 Hz), 129.2 (d, $J_{C,F}$ = 3.0 Hz), 129.4, 129.5, 129.7, 129.9, 129.9, 130.0, 130.2, 130.6, 132.7, 132.8, 139.9, 140.5 (d, $^3J_{C,F}$ = 1.1 Hz), 141.0, 142.5, 166.6, 166.7, 166.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –150.62 (dd, *J* = 31.4, 26.0 Hz), –145.19 to –144.79 (m), 134.15 (ddd, *J* = 34.4, 32.2, 16.4 Hz), –132.55 (dq, *J* = 36.8, 17.9 Hz), –127.61 (dd, *J* = 31.6, 19.1 Hz), –126.59 (td, *J* = 31.5, 16.4 Hz) ppm.

(1S*,2S*)-2-Fluoro-3-methyl-2,4′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl and (1S*,2S*)-2-Fluoro-6-methyl-2,4′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl (2p). Eluent: Hex/DCM (1:1), DCM; 0.195 g (69 %) obtained from 1.0 mmol of nitrostyrene 1n; pale brown oil. Anal. calcd. for $C_{13}H_{13}FN_2O_4$ (%): C, 55.71; H, 4.68; N, 10.00; found C, 55.75; H, 4.58; N, 9.89. Isomers ratio: 42:10:5:28:6:10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–1.17 (m, 6H), 1.47–1.88 (m, 1H), 2.48–2.90 (m, 4H), 3.04–3.50 (m, 2H), 3.72–4.25 (m, 1H), 5.48–5.99 (m, 4H), 7.29–7.59 (m, 4H), 8.08–8.27 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0 (d, $^3J_{C,F}$ = 6.7 Hz), 15.9 (d, $^3J_{C,F}$ = 4.2 Hz), 17.6 (d, $^3J_{C,F}$ = 7.4 Hz), 17.9 (d, $^3J_{C,F}$ = 6.7 Hz), 19.1, 31.0 (d, $^3J_{C,F}$ = 3.7 Hz), 32.6 (d, $^3J_{C,F}$ = 4.0 Hz), 35.3 (d, $^3J_{C,F}$ = 2.8 Hz), 35.8 (d, $^2J_{C,F}$ = 24.1 Hz), 35.9 (d, $^2J_{C,F}$ = 24.5 Hz), 36.1, 39.4 (d, $^2J_{C,F}$ = 22.1 Hz), 39.5 (d, $^2J_{C,F}$ = 24.0 Hz), 41.8 (d, $^2J_{C,F}$ = 19.6 Hz), 47.0 (d, $^2J_{C,F}$ = 20.0 Hz), 48.9 (d, $^2J_{C,F}$ = 17.8 Hz), 53.3 (d, $^2J_{C,F}$ = 19.3 Hz), 118.7, 119.3, 119.7, 120.5 (d, $^1J_{C,F}$ = 246.6 Hz), 122.3 (d, $^1J_{C,F}$ = 243.9 Hz), 123.8, 123.9, 123.9, 124.6, 125.0, 127.7, 128.0, 128.1, 128.9 (d, $^3J_{C,F}$ = 7.9 Hz), 129.9 (d, $J_{C,F}$ = 2.4 Hz), 130.1 (d, $J_{C,F}$ = 3.2 Hz), 130.2 (d, $J_{C,F}$ = 3.4 Hz), 130.4 (d, $J_{C,F}$ = 2.9 Hz), 132.4, 132.5, 142.3, 142.9 (d, $^3J_{C,F}$ = 1.2 Hz), 144.9, 147.6, 148.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –150.48 (dd, *J* = 30.7, 26.3 Hz), –145.01 (ddt, *J* = 43.1, 24.3, 18.5 Hz), –134.12 (ddd, *J* = 35.0, 31.0, 16.6 Hz), –133.75 to –133.21 (m), –127.86 (dd, *J* = 31.3, 19.3 Hz), –126.87 (td, *J* = 31.5, 16.5 Hz) ppm.

Synthesis of Isoprene Based Cycloadducts 2

(1′S*,2′S*)-Methyl 2′-Fluoro-4′-methyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carboxylate and (1′S*,2′S*)-Methyl 2′-Fluoro-5′-methyl-2′-nitro-1′,2′,3′,6′-tetrahydro-[1,1′-biphenyl]-4-carboxylate (2r) (59:31). Eluent: Hex/DCM (1:1), DCM; 0.124 g (85 %); colorless oil. Anal. calcd. for $C_{15}H_{16}FNO_4$ (%): C, 61.43; H, 5.50; N, 4.78; found C, 61.51; H, 5.49; N, 4.77; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 6H), 2.24–2.77 (m, 6H), 2.98–3.30 (m, 2H), 3.60–3.93 (m, 2H), 3.87 (s, 6H), 5.34–5.41 (m, 1H), 5.54–5.63 (m, 1H), 7.30–7.38 (m, 4H), 7.91–7.97 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 22.8, 30.6 (d, $^3J_{C,F}$ = 3.4 Hz), 35.4 (d, $^3J_{C,F}$ = 3.4 Hz), 36.1 (d, $^2J_{C,F}$ = 23.9 Hz), 40.2 (d, $^2J_{C,F}$ = 24.4 Hz), 45.9 (d, $^2J_{C,F}$ = 19.6 Hz), 46.2 (d, $^2J_{C,F}$ = 19.5 Hz), 52.2, 115.0, 120.0 (d, $^1J_{C,F}$ = 244.3 Hz), 120.2 (d, $^1J_{C,F}$ = 244.0 Hz), 120.3, 128.8, 128.9, 129.0, 129.7, 129.8, 129.9, 130.0, 130.1, 134.0, 141.0, 166.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.82 (ddd, *J* = 34.1, 31.3, 16.6 Hz, 1F), –134.73 (ddd, *J* = 34.0, 31.8, 16.6 Hz, 1F) ppm

(1S*,2S*)-2-fluoro-4-methyl-2,4′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl and (1S*,2S*)-2-fluoro-5-methyl-2,4′-dinitro-1,2,3,6-tetrahydro-1,1′-biphenyl (2s) (36:56). Eluent: Hex/DCM (1:1); 0.092 g; pale brown oil. Anal. calcd. for $C_{13}H_{13}FN_2O_4$ (%): C, 55.71; H, 4.68; N, 10.00; found C, 55.85; H, 4.77; N, 9.89; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 6H), 2.33–2.86 (m, 6H), 3.05–3.31 (m, 2H), 3.70–4.00 (m, 2H), 5.37–5.45 (m, 1H), 5.58–5.64 (m, 1H), 7.42–7.51 (m, 4H), 8.09–8.18 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.3, 30.1 (d, $^3J_{C,F}$ = 3.4 Hz), 34.9 (d, $^3J_{C,F}$ = 3.3 Hz), 35.5 (d, $^2J_{C,F}$ = 23.9 Hz), 39.6 (d, $^2J_{C,F}$ = 24.3 Hz), 45.3 (d, $^2J_{C,F}$ = 19.6 Hz), 45.6 (d, $^2J_{C,F}$ = 19.8 Hz), 114.6, 119.2 (d, $^1J_{C,F}$ = 244.3 Hz), 119.4, 119.5 (d, $^1J_{C,F}$ = 244.1 Hz), 123.1, 123.2, 123.3, 123.4, 128.5, 129.4, 133.2, 142.8, 147.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –135.81 (ddd, *J* = 34.7, 30.6, 16.8 Hz, 1F), –134.72 (ddd, *J* = 34.6, 30.7, 16.8 Hz, 1F).

Synthesis of 3-(4-Chlorophenyl)-4-fluoro-5-methoxy-4-nitrocyclohexanone and 3-(4-Chlorophenyl)-4-fluoro-2-methoxy-4-nitrocyclohexanone (5f).

β-Fluoro-β-nitrostyrene **1f** (0.101 mg, 0.5 mmol), *o*-xylene (0.2 mL) and Danishefsky's diene (0.48 mL, 2.5 mmol) were successively loaded into a screw-top vial filled with argon. After the cap was screwed tightly, the reaction mixture was heated at 110 °C with vigorous stirring for 7.5 h. After completion of the cycloaddion (TLC monitoring), the reaction mixture was treated with HCl/THF (1:1) solution (2 mL) at 0 °C for 1h. Then the acid excess was neutralized with saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with DCM. The combined organic layer was dried with Na_2SO_4, filtered and concentrated under vacuum. Purification by column chromatography on silica gel using DCM as eluent gave the product **5f** (0.115 g, 76 %) as mixture of isomers. Yellowish oil; isomers ratio: 56:29:6:4:4. Anal. calcd. for $C_{13}H_{13}ClFNO_4$ (%): C, 51.75; H, 4.34; N, 4.64; found C, 51.69; H, 4.30; N, 4.29; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59–2.71 (m, 2H), 2.76–2.87 (m, 2H), 2.88–3.11 (m, 4H), 3.37 (s, 3H), 3.38 (s, 3H), 3.67–3.83 (m, 1H), 4.12–4.19 (m, 1H), 4.29–4.50 (m, 2H), 7.14–7.20 (m, 4H), 7.28–7.33 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.4, 42.3 (d, $^2J_{C,F}$ = 17.4 Hz), 42.8 (d, $^3J_{C,F}$ = 1.2 Hz), 43.2 (d, $^3J_{C,F}$ = 2.8 Hz), 44.3 (d, $^3J_{C,F}$ = 1.8 Hz), 44.7 (d, $^2J_{C,F}$ = 19.0 Hz), 58.4, 58.5, 78.8 (d, $^2J_{C,F}$ = 18.7 Hz), 80.1 (d, $^2J_{C,F}$ = 29.7 Hz), 117.6 (d, $^1J_{C,F}$ = 240.3 Hz), 118.6 (d, $^1J_{C,F}$ = 248.2 Hz), 129.2, 129.5, 129.8 (d, $^4J_{C,F}$ = 1.8 Hz), 130.6 (d, $^4J_{C,F}$ = 2.6 Hz), 130.8, 133.1, 134.6, 135.3, 201.7, 202.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –157.98 (dd, *J* = 28.7, 20.8 Hz), –140.19 (d, *J* = 33.0 Hz), –134.09 (t, *J* = 11.1 Hz), –125.72 (t, *J* = 8.7 Hz), –116.78 (t, *J* = 10.3 Hz) ppm.

General Procedure for Synthesis of Biphenyls

In a typical experiment, a solution of cycloadduct (0.20 mmol; 1 mol. equiv.) in acetonitrile (0.5 mL) was loaded into a glass tube and treated with DBU (0.8–1.6 mmol; 4–8 mol equiv.) at 60 °C with vigorous stirring using either compressed air (1.5 bar; Method 1) or MnO_2 (5 mol. equiv.; Method 2) as oxidant. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under vacuum. The resulting mixture was separated by column chromatography using mixture of Hex/DCM as eluent.

4′-(*tert*-Butyl)-4,5-dimethyl-2-nitro-1,1′-biphenyl (**4b**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1, 0.015 g (27 %), pale-

yellow solid; M.p. 116–118 °C (Hex/DCM, 5:1). Anal. calcd. for. $C_{18}H_{21}NO_2$ (%): C, 76.29; H, 7.47; N, 4.94; found C, 76.05; H, 7.48; N, 4.75. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.35 (s, 3H), 2.36 (s, 3H), 7.19 (s, 1H), 7.23 (d, $J_{H,H}$ = 8.4 Hz, 2H), 7.42 (d, $J_{H,H}$ = 8.4 Hz, 2H), 7.65 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 31.5, 34.8, 125.2, 125.6, 127.8, 133.2, 134.1, 134.8, 136.9, 142.0, 147.1, 151.0 ppm.

4,4′,5-Trimethyl-2-nitro-1,1′-biphenyl (**4c**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1. 0.036 g (41 %), pale yellow oil. Anal. calcd. for. $C_{15}H_{15}NO_2$ (%):C, 74.67; H, 6.27; N, 5.81; found C, 74.70; H, 6.25; N, 5.74 ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.37 (s, 3H), 2.40 (s, 3H), 7.17–7.25 (m, 5H), 7.67 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 21.3, 125.2, 127.9, 129.4, 133.1, 134.1, 134.9, 136.9, 137.8, 142.1, 146.9 ppm.

4,5-Dimethyl-2-nitro-1,1′-biphenyl (**4d**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1, 0.007 g (16 %), yellow oil. Anal. calcd. for. $C_{14}H_{13}NO_2$ (%):C, 73.99; H, 5.77; N, 6.16; found C, 73.36; H, 5.78; N, 5.99. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.37 (s, 3H), 7.18 (s, 1H), 7.27–7.32 (m, 2H), 7.34–7.45 (m, 3H), 7.69 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 125.3, 128.0, 128.1, 128.7, 133.2, 134.2, 137.2, 138.0, 142.2, 147.0 ppm.

4′-Fluoro-4,5-dimethyl-2-nitro-1,1′-biphenyl (**4e**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1; 0.015 g (30 %), pale yellow oil. Anal. calcd. for. $C_{14}H_{12}FNO_2$ (%):C, 68.56; H, 4.93; N, 5.71 Found: C, 68.48; H, 5.05; N, 5.68. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.37 (s, 3H), 7.06–7.13 (m, 2H), 7.15 (s, 1H), 7.22–7.28 (m, 2H), 7.70 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 115.7 (d, $^2J_{C,F}$ = 21.8 Hz), 125.4, 129.8 (d, $^3J_{C,F}$ = 8.2 Hz), 133.1, 133.9, 133.9, 137.5, 142.4, 146.8, 162.7 (d, $^1J_{C,F}$ = 247.1 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.31 (tt, J = 8.6, 5.2 Hz) ppm.

4′-Chloro-4,5-dimethyl-2-nitro-1,1′-biphenyl (**4f**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1, 0.020 g (38 %), yellowish oil. Anal. calcd. for. $C_{14}H_{12}ClNO_2$ (%):C, 64.25; H, 4.62; N, 5.35; found C, 64.59; H, 4.54; N, 5.38; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.37 (s, 3H), 7.13 (s, 1H), 7.18–7.23 (m, 2H), 7.35–7.40 (m, 3H), 7.71 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 125.5, 128.9, 129.5, 133.0, 133.1, 134.2, 136.5, 137.7, 142.5, 146.6 ppm.

4′-Bromo-4,5-dimethyl-2-nitro-1,1′-biphenyl (**4g**). Eluent: Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1; 0.019 g (32 %), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.37 (s, 3H), 7.13 (s, 1H), 7.15 (d, $J_{H,H}$ = 8.4 Hz, 2H), 7.53 (d, $J_{H,H}$ = 8.4 Hz, 2H), 7.72 (s, 1H) ppm. Analysis of the sample was consistent with the data reported in the literature.[35]

Biphenyls 3h and 4h. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 3:1; Hex/DCM, 3:2) gave the target product **3h** and the side product **4h**.

Methyl 2′-fluoro-4′,5′-dimethyl-[1,1′-biphenyl]-4-carboxylate (**3h**). Method 1: 0.031 g (73 %); method 2: 0.009 g (77 %) obtained from 0.047 mmol of cycloadduct **2h**; colorless solid; M.p. 99–101 °C (Hex/DCM, 3:1). Anal. calcd. for $C_{16}H_{15}FO_2$: C, 74.40; H, 5.85; found C, 74.45; H, 5.81. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.29 (s, 3H), 3.94 (s, 3H), 6.96 (d, $^3J_{H,F}$ = 11.5 Hz, 1H), 7.21 (d, $^4J_{H,F}$ = 8.0 Hz, 1H), 7.59–7.63 (m, 2H), 8.07–8.11 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 19.8, 52.3, 117.3 (d, $^2J_{C,F}$ = 22.4 Hz), 124.9 (d, $^2J_{C,F}$ = 12.9 Hz), 129.0 (d, $^4J_{C,F}$ = 3.3 Hz), 129.7, 129.8, 131.3 (d, $^3J_{C,F}$ = 3.5 Hz), 132.7 (d, $^3J_{C,F}$ = 3.4 Hz), 138.9 (d, $^3J_{C,F}$ = 8.0 Hz), 140.8 (d, $^4J_{C,F}$ = 1.2 Hz), 158.0 (d, $^1J_{C,F}$ = 246.0 Hz), 167.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –123.18 to –123.07 (m) ppm.

Methyl 4′,5′-dimethyl-2′-nitro-[1,1′-biphenyl]-4-carboxylate (**4h**). Method 1: 0.004 g (8 %); method 2: 0.001 g (6 %) obtained from 0.047 mmol of cycloadduct **2h**; pale-yellow solid; M.p. 106–108 °C (Hex/DCM, 3:2). Anal. calcd. for. $C_{16}H_{15}NO_4$ (%): C, 67.36; H, 5.30; N, 4.91; found C, 67.33; H, 5.73; N, 4.90. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.38 (s, 3H), 3.94 (s, 3H), 7.16 (s, 1H), 7.33–7.37 (m, 2H), 7.76 (s, 1H), 8.06–8.10 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 19.9, 52.3, 125.6, 128.2, 129.7, 129.9, 132.9, 133.4, 138.0, 142.6, 142.9, 166.9 ppm.

Biphenyls 3i and 4i. purification by column chromatography on silica gel with gradient elution (Hex/DCM, 5:1; Hex/DCM, 3:1) gave the target product **3i** and the side product **4i**.

2-Fluoro-4,5-dimethyl-4′-(trifluoromethyl)-1,1′-biphenyl (**3i**). Method 1: 0.032 g (59 %); method 2: 0.029 g (55 %); colorless solid; M.p. 56–58 °C (Hex/DCM, 5:1). Anal. calcd. for $C_{15}H_{12}F_4$: C, 67.16; H, 4.51; found C, 67.21; H, 4.59. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.30 (s, 3H), 6.97 (d, $^3J_{H,F}$ = 11.4 Hz, 1H), 7.19 (d, $^4J_{H,F}$ = 8.0 Hz, 1H), 7.64 (d, $^3J_{H,H}$ = 8.5 Hz, 2H), 7.68 (d, $^3J_{H,H}$ = 8.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.8, 117.3 (d, $^2J_{C,F}$ = 22.3 Hz), 124.4 (q, $^1J_{C,F}$ = 272.0 Hz), 124.6 (d, $^2J_{C,F}$ = 12.9 Hz), 125.4 (q, $^3J_{C,F}$ = 3.7 Hz), 129.3 (d, $^4J_{C,F}$ = 3.0 Hz), 129.4 (q, $^2J_{C,F}$ = 32.6 Hz), 131.4 (d, $^3J_{C,F}$ = 3.3 Hz), 132.8 (d, $^3J_{C,F}$ = 3.5 Hz), 139.0 (d, $^3J_{C,F}$ = 7.7 Hz), 139.8, 158.0 (d, $^1J_{C,F}$ = 246.1 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –123.43 to –123.34 (m, 1F), –62.50 (s, 3F) ppm.

4,5-Dimethyl-2-nitro-4′-(trifluoromethyl)-1,1′-biphenyl (**4i**). Method 1: 0.006 g (10 %); method 2: 0.011 (19 %); yellowish oil. Anal. calcd. for $C_{15}H_{12}F_3NO_2$: C, 61.02; H, 4.10; N, 4.74; found C, 61.24; H, 4.23; N, 4.73; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 2.39 (s, 3H), 7.15 (s, 1H), 7.40 (d, $J_{H,H}$ = 8.1 Hz, 2H), 7.66 (d, $J_{H,H}$ = 8.1 Hz, 2H), 7.77 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 20.0, 121.5 (q, $^1J_{C,F}$ = 272.1 Hz), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz), 125.6, 128.5, 128.6, 130.1 (q, $^2J_{C,F}$ = 32.6 Hz), 133.0, 138.2, 141.9, 142.8, 146.5 ppm; ^{19}F NMR (376 MHz,$CDCl_3$): δ = –63.55 ppm.

Biphenyls 3j and 4j. Separation by column chromatography on silica gel with gradient elution (Hex/DCM, 10:1; Hex/DCM, 5:1; Hex/DCM, 2:1) gave the fraction predominantly contained non-oxidized intermediate of **3j** (**IM-1**) and the fraction with the pure side product **4j**. Then the solid residue from the first fraction (0.011 g) was treated with MnO_2 (0.018 g, 5 mol. equiv.) in toluene (0.2 mL) at 80 °C for 5 h. Purification of the resulting mixture by column chromatography on silica gel using hexane as eluent afforded pure **3j**.

2′,4′-Dichloro-2-fluoro-4,5-dimethyl-1,1′-biphenyl (**3j**). 0.008 g (15 %); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.30 (s, 3H), 6.94 (d, $^3J_{H,F}$ = 10.4 Hz, 1H), 7.01 (d, $^4J_{H,F}$ = 7.6 Hz, 1H), 7.24 (d, $^3J_{H,H}$ = 8.3 Hz, 1H), 7.29 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H), 7.49 (d, $^4J_{H,H}$ = 2.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 19.9, 116.7 (d, $^2J_{C,F}$ = 21.7 Hz), 122.9 (d, $^2J_{C,F}$ = 15.6 Hz), 127.1, 129.5, 132.1 (d, $^3J_{C,F}$ = 3.1 Hz), 132.2 (d, $^3J_{C,F}$ = 3.3 Hz), 132.6, 133.9, 134.3, 134.7, 139.2 (d, $^3J_{C,F}$ = 7.6 Hz), 157.7 (d, $^1J_{C,F}$ = 244.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –119.72 to –119.62 (m) ppm.

2′,4′-Dichloro-4,5-dimethyl-2-nitro-1,1′-biphenyl (**4j**). Method 1: 0.016 g (26 %); pale-yellow solid; M.p. 130–132 °C (Hex/DCM, 5:1). Anal. calcd. for. $C_{14}H_{11}Cl_2NO_2$ (%):C, 56.78; H, 3.74; N, 4.73; found C, 56.72; H, 3.68; N, 4.72. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.40 (s, 3H), 7.06 (s, 1H), 7.18 (d, $^3J_{H,H}$ = 8.2 Hz, 1H), 7.31 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 2.1 Hz, 1H), 7.46 (d, $^4J_{H,H}$ = 2.1 Hz, 1H), 7.94 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 20.0, 125.7, 127.3, 129.3, 130.8, 131.0, 133.3, 133.8, 134.4, 136.4, 138.6, 143.4, 146.1 ppm.

4,5-Dimethyl-2,2′-dinitro-1,1′-biphenyl (**4k**). Eluent: Hex/DCM (4:1); Hex/DCM, 2:1; method 1: 0.023 g (42 %); method 2: 0.024 g (44 %); pale brown solid; M.p. 100–102 °C (Hex/DCM, 2:1). Anal. calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29; found C, 61.68; H,

4.57; N, 10.10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 2.40 (s, 3H), 7.03 (s, 1H), 7.27 (d, $^3J_{H,H}$ = 7.4 Hz, 1H), 7.56 (dd, $^3J_{H,H}$ = 8.0, 7.6 Hz, 1H), 7.66 (dd, $^3J_{H,H}$ = 7.6, 7.4 Hz, 1H), 8.02 (s, 1H), 8.18 (d, $^3J_{H,H}$ = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 20.0, 124.8, 125.9, 128.9, 131.2, 131.7, 131.9, 133.4, 134.7, 138.3, 143.7, 145.0, 147.5 ppm.

Biphenyls 3l and 4l. purification by column chromatography on silica gel with gradient elution (Hex/DCM, 4:1; Hex/DCM, 3:1) gave the target product **3l** and the side product **4l**.

2-Fluoro-4,5-dimethyl-3′-nitro-1,1′-biphenyl (**3l**). Method 1: 0.020 g (41 %), method 2: 0.024 g (49 %); colorless solid; M.p. 78–80 °C (Hex/DCM, 4:1). Anal. calcd. for $C_{14}H_{12}FNO_2$: C, 68.56; H, 4.93; N, 5.71; found C, 68.60; H, 4.95; N, 5.55. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.31 (s, 3H), 6.98 (d, $^3J_{H,F}$ = 11.4 Hz, 1H), 7.22 (d, $^4J_{H,F}$ = 8.0 Hz, 1H), 7.59 (t, $^3J_{H,H}$ = 7.9 Hz, 1H), 7.88 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H), 8.16–8.25 (m, 1H), 8.40 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.9, 117.4 (d, $^2J_{C,F}$ = 22.2 Hz), 122.2, 123.5 (d, $^2J_{C,F}$ = 12.7 Hz), 123.8 (d, $^4J_{C,F}$ = 3.0 Hz), 129.4, 131.2 (d, $^3J_{C,F}$ = 3.0 Hz), 133.1 (d, $^3J_{C,F}$ = 3.4 Hz), 135.1 (d, $^4J_{C,F}$ = 3.6 Hz), 137.8, 139.5 (d, $^3J_{C,F}$ = 7.9 Hz), 148.5, 157.9 (d, $^1J_{C,F}$ = 246.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.64 to –124.50 (m) ppm.

4,5-Dimethyl-2,3′-dinitro-1,1′-biphenyl (**4l**). Method 1: 0.009 g (17 %); method 2: 0.015 g (27 %), pale yellow solid; M.p. 158–160 °C (Hex/DCM, 3:1). Anal. calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29; found C, 61.84; H, 4.52; N, 10.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 2.40 (s, 3H), 7.17 (s, 1H), 7.54–7.61 (m, 2H), 7.84 (s, 1H), 8.19 (s, 1H), 8.21–8.30 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 20.0, 122.9, 123.3, 125.9, 128.2, 129.5, 132.1, 133.1, 134.4, 138.7, 140.0, 143.2, 143.3 ppm.

Biphenyls 3m and 4m. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 2:1; Hex/DCM, 1:1; Hex/DCM, 1:2) gave the target product **3m** and the side product **4m**.

2′-Fluoro-4′,5′-dimethyl-[1,1′-biphenyl]-4-carbonitrile (**3m**). Method 1:0.030 g (67 %); method 2: 0.032 (70 %); colorless solid; M.p. 106–108 °C (Hex/DCM, 2:1). Anal. calcd. for $C_{15}H_{12}FN$: C, 79.98; H, 5.37; N, 6.22; found C, 79.80; H, 5.32; N, 6.14. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.30 (s, 3H), 6.97 (d, $^3J_{H,F}$ = 11.5 Hz, 1H), 7.17 (d, $^4J_{H,F}$ = 8.0 Hz, 1H), 7.64 (dd, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 1.4 Hz, 2H), 7.67–7.73 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 19.8, 111.0, 117.4 (d, $^2J_{C,F}$ = 22.4 Hz), 119.1, 124.0 (d, $^2J_{C,F}$ = 12.6 Hz), 129.6 (d, $^4J_{C,F}$ = 3.4 Hz), 131.1 (d, $^3J_{C,F}$ = 3.2 Hz), 132.3, 133.0 (d, $^3J_{C,F}$ = 3.3 Hz), 139.6 (d, $^3J_{C,F}$ = 8.0 Hz), 140.9 (d, $^4J_{C,F}$ = 1.0 Hz), 157.9 (d, $^1J_{C,F}$ = 246.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.07 (t, J = 9.3 Hz) ppm.

4′,5′-Dimethyl-2′-nitro-[1,1′-biphenyl]-4-carbonitrile (**4m**). Eluent: Hex/DCM; method 1: 0.002 g (3 %); method 1: 0.005 g (10 %), colorless solid; M.p. 161–163 °C (Hex/DCM, 1:2). Anal. calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; found C, 71.43; H, 4.72; N, 10.98. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 2.39 (s, 3H), 7.13 (s, 1H), 7.36–7.41 (m, 2H), 7.68–7.72 (m, 2H), 7.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 19.9, 112.0, 118.7, 125.8, 129.0, 132.4, 132.7, 132.8, 138.6, 143.0, 143.1, 146.3 ppm.

2-Fluoro-4,5-dimethyl-4′-nitro-1,1′-biphenyl (3n); Eluent: Hex/DCM (2:1); method 1: 0.045 g (92 %), method 2: 0.042 g (86 %); yellow solid; M.p. 105–107 °C (Hex/DCM, 2:1). HRMS (ESI): calcd. for $C_{14}H_{11}FNO_2$ $[M - H]^-$ = 244.0774, found 244.0780; calcd. for $C_{14}H_{13}FNO_2$ $[M + H]^+$ = 246.0930, found 246.0923; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.31 (s, 3H), 6.98 (d, $^3J_{H,F}$ = 11.0 Hz, 1H), 7.21 (d, $^4J_{H,F}$ = 8.4 Hz, 1H), 7.65–7.73 (m, 2H), 8.25–8.30 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.9, 117.5 (d, $^2J_{C,F}$ = 22.3 Hz), 123.7 (d, $^2J_{C,F}$ = 10.1 Hz), 123.8, 129.7 (d, $^4J_{C,F}$ = 3.4 Hz), 131.2 (d, $^3J_{C,F}$ = 3.0 Hz), 133.1 (d, $^3J_{C,F}$ = 3.3 Hz), 140.0 (d, $^3J_{C,F}$ = 8.0 Hz), 142.9 (d, $^4J_{C,F}$ = 1.1 Hz), 147.0, 157.9 (d, $^1J_{C,F}$ = 246.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –122.85 (dd, J = 11.0, 8.4 Hz) ppm.

Biphenyls 3o and 4o. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 2:1; Hex/DCM, 1:1; DCM) gave the target products mixture **3o** and the side products mixture **4o**.

Methyl 2′-fluoro-3′-methyl-[1,1′-biphenyl]-4-carboxylate and **methyl 2′-fluoro-6′-methyl-[1,1′-biphenyl]-4-carboxylate** (**3o**) (48:52). Method 1: 0.023 g (25 %); method 2: 0.025 g (26 %), colorless oil. Anal. calcd. for. $C_{15}H_{13}FO_2$ (%):C, 73.76; H, 5.36; found C, 73.51; H, 5.60; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3H); 2.35 (d, J = 2.2 Hz, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.99 (t, J = 8.8 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.18–7.29 (m, 3H), 7.37 (d, J = 8.1 Hz, 2H), 7.62 (dd, J = 8.4, 1.6 Hz, 2H), 8.08–8.14 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (d, $^3J_{C,F}$ = 5.0 Hz), 20.2 (d, $^4J_{C,F}$ = 2.9 Hz), 52.3, 52.4, 113.1 (d, $^2J_{C,F}$ = 22.8 Hz), 124.1 (d, $^3J_{C,F}$ = 4.4 Hz), 125.8 (d, $^2J_{C,F}$ = 18.1 Hz), 125.9 (d, $^4J_{C,F}$ = 3.3 Hz), 127.8 (d, $^2J_{C,F}$ = 14.3 Hz), 128.3 (d, $^4J_{C,F}$ = 3.1 Hz), 128.5 (d, $^2J_{C,F}$ = 15.8 Hz), 129.0 (d, $^3J_{C,F}$ = 8.9 Hz), 129.1, 129.2, 129.4, 129.6, 129.7, 130.2, 131.5 (d, $^3J_{C,F}$ = 5.2 Hz), 138.4 (d, $^3J_{C,F}$ = 2.4 Hz), 139.9, 140.9, 158.3 (d, $^1J_{C,F}$ = 247.6 Hz), 158.9 (d, $^1J_{C,F}$ = 244.7 Hz), 167.0, 167.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –121.97 to –121.86 (m, 1F), –115.36 (dd, J = 9.3, 5.8 Hz, 1F) ppm.

Methyl 2′-methyl-6′-nitro-[1,1′-biphenyl]-4-carboxylate and **methyl 3′-methyl-2′-nitro-[1,1′-biphenyl]-4-carboxylate** (**4o**) (23:77). Method 1: 0.005 g (5 %); method 2: 0.005 g (5 %); pale yellow oil. Anal. calcd. for. $C_{15}H_{13}NO_4$ (%): C, 66.41; H, 4.83; N, 5.16; found C, 66.62; H, 4.92; N, 5.09; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 6H), 3.90 (s, 3H), 3.94 (s, 3H), 7.26–7.30 (m, 4H), 7.34–7.37 (m, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.09–8.14 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 52.4, 121.6, 128.5, 128.7, 129.8, 130.0, 134.3, 134.8, 139.0, 141.3, 149.9, 166.9 ppm.

Biphenyls 3p and 4p. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 2:1; Hex/DCM, 1:1) gave the target products mixture **3p** and the side products mixture **4p**.

2-Fluoro-3-methyl-4′-nitro-1,1′-biphenyl and **2-fluoro-6-methyl-4′-nitro-1,1′-biphenyl** (**3p**) (34:66). Method 1: 0.020 g (40 %); method 2: 0.051 g (46 %) obtained from 0.47 mmol of cycloadduct **2p**; pale yellow solid; M.p. 59–74 °C (Hex/DCM, 2:1). Anal. calcd. for. $C_{13}H_{10}FNO_2$ (%):C, 67.53; H, 4.36; N, 6.06, Found: C, 67.42; H, 4.36; N, 5.91; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3H), 2.36 (d, J = 2.2 Hz, 3H), 7.01 (t, J = 8.8 Hz, 1H), 7.08–7.18 (m, 2H), 7.23–7.33 (m, 3H), 7.47 (d, J = 8.3 Hz, 2H), 7.71 (dd, J = 8.8, 1.5 Hz, 2H), 8.27–8.33 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (d, $^3J_{C,F}$ = 4.8 Hz), 20.2 (d, $^4J_{C,F}$ = 2.8 Hz), 113.2 (d, $^2J_{C,F}$ = 22.5 Hz), 123.6, 123.7, 124.3 (d, $^3J_{C,F}$ = 4.5 Hz), 126.1 (d, $^4J_{C,F}$ = 3.3 Hz), 126.2 (d, $^2J_{C,F}$ = 18.1 Hz), 126.6 (d, $^2J_{C,F}$ = 13.8 Hz), 127.3 (d, $^2J_{C,F}$ = 15.6 Hz), 128.1 (d, $^4J_{C,F}$ = 2.8 Hz), 129.7 (d, $^3J_{C,F}$ = 9.0 Hz), 130.0 (d, $^4J_{C,F}$ = 3.5 Hz), 131.2, 132.3 (d, $^3J_{C,F}$ = 5.4 Hz), 138.2 (d, $^3J_{C,F}$ = 2.2 Hz), 142.0, 143.0, 147.2, 147.4, 158.2 (d, $^1J_{C,F}$ = 248.3 Hz), 159.6 (d, $^1J_{C,F}$ = 245.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –121.69 (td, J = 7.0, 2.1 Hz, 1F), –115.24 (dd, J = 9.4, 5.8 Hz, 1F) ppm.

2-Methyl-4′,6-dinitro-1,1′-biphenyl and **3-methyl-2,4′-dinitro-1,1′-biphenyl** (**4p**) (87:13). Method 2: 0.005 g (4 %) obtained from 0.47 mmol of cycloadduct **2p**; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 2.20 (s, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.36–7.41 (m, 2H), 7.45–7.59 (m, 4H), 7.83 (d, J = 8.0 Hz, 2H), 8.25–8.36

(m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 122.0, 123.7, 124.1, 129.1, 129.6, 131.2, 133.7, 134.8, 138.8, 143.7 ppm.

Biphenyls 3r and 4r. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 2:1; Hex/DCM, 1:1) gave the target products mixture **3r** and the side products mixture **4r**.

Methyl 2′-fluoro-5′-methyl-[1,1′-biphenyl]-4-carboxylate and **methyl 2′-fluoro-4′-methyl-[1,1′-biphenyl]-4-carboxylate** (**3r**) (58:42). Method 1: 0.028 g (27 %); method 2: 0.031 g (37 %) (Method 2); viscous colorless oil. Anal. calcd. for. $C_{15}H_{13}FO_2$ (%): C, 73.76; H, 5.36; found C, 73.90; H, 5.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.40 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.99 (d, J = 11.8 Hz, 1H), 7.02–7.09 (m, 2H), 7.11–7.17 (m, 1H), 7.22–7.25 (m, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.60–7.64 (m, 4H), 8.10 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.2 (d, $^4J_{C,F}$ = 1.0 Hz), 52.2, 52.3, 116.1 (d, $^2J_{C,F}$ = 22.6 Hz), 116.9 (d, $^2J_{C,F}$ = 22.5 Hz), 125.0 (d, $^2J_{C,F}$ = 13.1 Hz), 125.4 (d, $^3J_{C,F}$ = 3.0 Hz), 127.6 (d, $^2J_{C,F}$ = 13.4 Hz), 129.0 (d, $^3J_{C,F}$ = 3.3 Hz), 129.1 (d, $^4J_{C,F}$ = 3.1 Hz), 129.2, 129.7, 129.8, 130.3, 130.4, 130.4, 131.1 (d, $^4J_{C,F}$ = 3.0 Hz), 134.1 (d, $^3J_{C,F}$ = 3.7 Hz), 140.6 (d, $^3J_{C,F}$ = 1.1 Hz), 140.7 (d, $^3J_{C,F}$ = 8.2 Hz), 140.7, 158.1 (d, $^1J_{C,F}$ = 245.9 Hz), 159.7 (d, $^1J_{C,F}$ = 248.6 Hz), 167.0, 167.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –123.02 to –122.92 (m, 1F), –118.51 to –118.43 (m, 1F) ppm.

Methyl 5′-methyl-2′-nitro-[1,1′-biphenyl]-4-carboxylate and **methyl 4′-methyl-2′-nitro-[1,1′-biphenyl]-4-carboxylate** (**4r**) (78:22). Method 1: 0.010 g (9 %); method 2: 0.011 g (11 %); yellow solid; M.p. 109–122 °C (Hex/DCM, 1:1). Anal. calcd. for. $C_{15}H_{13}NO_4$ (%): C, 66.41; H, 4.83; N, 5.16; found C, 66.65; H, 4.96; N, 5.06; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H), 2.48 (s, 3H), 3.94 (s, 6H), 7.21 (d, J = 1.1 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 7.35–7.38 (m, 4H), 7.45 (dd, J = 7.8, 0.5 Hz, 1H), 7.73 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 8.05–8.11 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.6, 52.4, 52.4, 124.8, 124.9, 128.1, 128.2, 129.4, 129.5, 129.7, 129.8, 129.9, 130.0, 131.7, 132.5, 132.8, 133.5, 135.9, 139.6, 142.4, 142.8, 144.0, 148.9, 166.8, 166.8 ppm.

Biphenyls 3s and 4s. Purification by column chromatography on silica gel with gradient elution (Hex/DCM, 2:1; Hex/DCM, 1:1) gave the target products mixture **3s** and the side products mixture **4s**.

2-Fluoro-5-methyl-4′-nitro-1,1′-biphenyl and **2-fluoro-4-methyl-4′-nitro-1,1′-biphenyl** (**3s**) (42:58). Method 1: 0.064 g (86 %) obtained from 0.32 mmol of cycloadduct **2s**; method 2: 0.041 g (65 %) obtained from 0.27 mmol of cycloadduct **2s**; pale yellow oil. Anal. calcd. for. $C_{13}H_{10}FNO_2$ (%):C, 67.53; H, 4.36; N, 6.06; found C, 67.58; H, 4.36; N, 6.20. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 2.41 (s, 3H), 7.02 (d, J = 11.8 Hz, 1H), 7.05–7.12 (m, 2H), 7.16–7.27 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.57–7.76 (m, 4H), 8.24–8.31 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.3 (d, $^4J_{C,F}$ = 1.1 Hz), 116.3 (d, $^2J_{C,F}$ = 22.4 Hz), 117.1 (d, $^2J_{C,F}$ = 22.2 Hz), 123.7, 123.8, 123.9, 125.7 (d, $^3J_{C,F}$ = 3.3 Hz), 126.4 (d, $^2J_{C,F}$ = 13.1 Hz), 129.7 (d, $^3J_{C,F}$ = 3.5 Hz), 129.9 (d, $^4J_{C,F}$ = 3.4 Hz), 130.3 (d, $^4J_{C,F}$ = 3.4 Hz), 131.0 (d, $^4J_{C,F}$ = 2.6 Hz), 131.2 (d, $^4J_{C,F}$ = 8.1 Hz), 134.4 (d, $^3J_{C,F}$ = 3.7 Hz), 141.7 (d, $^3J_{C,F}$ = 8.4 Hz), 142.7 (d, $^3J_{C,F}$ = 7.4 Hz), 147.0, 147.2, 158.0 (d, $^1J_{C,F}$ = 247.0 Hz), 159.6 (d, $^1J_{C,F}$ = 249.3 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.10 to –121.62 (m, 1F), –118.25 to –118.17 (m, 1F) ppm.

5-Methyl-2,4′-dinitro-1,1′-biphenyl (**4s**). Method 2: 0.003 g (4 %); pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.43–7.48 (m, 2H), 7.50 (dd, J = 7.8, 0.9 Hz, 1H), 7.81 (d, J = 0.7 Hz, 1H), 8.26–8.31 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 124.0, 125.2, 129.2, 131.6, 131.8, 133.8, 140.5, 140.8, 142.9, 144.7 ppm.

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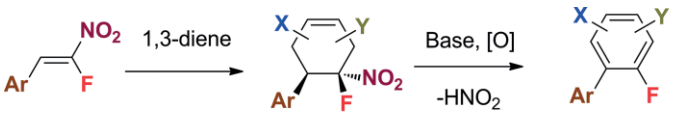
Fluorinated Nitrostyrenes



1 **2** up to 90 % **3** up to 92 %

TOC Text: The Diels-Alder reaction of β-fluoro-β nitrostyrenes with some linear dienes is reported. The kinetic studies were carried out to reveal substituent effect and activation parameters of the reaction. A new family of monofluorinated cyclohexenes **2** was prepared. The further transformation of **2** into biphenyls **3** based on base-induced elimination of HNO_2 followed by oxidative aromatization were described.

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